Health literacy, cognitive ability, and health

Chloe Fawns-Ritchie

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Dedicated to Zac

Declaration

I declare that the thesis has been composed by myself and that the work has not been submitted for any other degree or professional qualification. I confirm that the work submitted is my own, except where work which has formed part of jointly-authored publications has been included. My contribution and those of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

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Ritchie (student), John M Starr (supervisor) and Ian J Deary (supervisor). Conception and design of the study: **CF-R**, JMS, IJD. Data analysis: **CF-R**. Drafted the paper: **CF-R**. Revised the paper: **CF-R**. JMS, IJD. Approved the final version of the paper: **CF-R**, JMS, IJD.

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Chloe Fawns-Ritchie

Abstract

Poorer health literacy—the ability to acquire, understand and use health information to make better health decisions—has been associated with worse health outcomes. Poorer cognitive ability has also been found to predict increased risk of morbidity and mortality. Health literacy is often assessed using brief tests of health-related reading comprehension and numeracy. Scores on tests of health literacy have moderate-to-strong correlations with cognitive ability test scores. Despite this, few studies have investigated the associations of both health literacy and cognitive ability with respect to health outcomes. This thesis examined whether health literacy and cognitive ability, when studied together, have unique associations with health.

The first study in this thesis investigated the unique contributions of health literacy and cognitive ability to smoking status in a sample of 8,734 middle-aged and older adults from the English Longitudinal Study of Ageing (ELSA). Limited health literacy (OR=1.13, 95% CI 1.03-1.25) and poorer cognitive ability (OR per SD=0.94, 95% CI 0.89-0.99) were associated with increased odds of reporting ever smoking. These associations were attenuated and non-significant after adjusting for education and social class. In participants who reported ever smoking, limited health literacy (OR=1.34, 95% CI 1.17-1.54) and poorer cognitive ability (OR=0.88, 95% CI 0.81-0.95) were associated with being a current smoker, and this remained significant even after adjusting for socioeconomic variables.

The second study investigated whether health literacy and cognitive ability were independently associated with diabetes, using a sample of ELSA participants (n=8,669). When examined concurrently, adequate health literacy (OR=0.82, 95% CI 0.69-0.98) and higher cognitive ability (OR per SD=0.78, 95% CI 0.70-0.86) were independently associated with lower odds of self-reported diabetes. Adjusting for

health behaviours attenuated these associations and they were no longer significant. Individuals who did not have diabetes were then followed up for up to 10 years. Adequate health literacy (HR=0.72, 95% CI 0.59-0.87) and higher cognitive ability (HR=0.79, 95% CI 0.71-0.88) were associated with a lower risk of developing diabetes. These associations were attenuated by health behaviours and education.

The third study sought to determine the role of cognitive ability, measured in childhood and in older age, in the association between health literacy and mortality. Using data from 795 elderly participants from the Lothian Birth Cohort 1936, this study found that lower scores on two tests of health literacy—the Newest Vital Sign (OR per 1 point increase=0.89, 95% CI 0.80-0.99) and the shortened Test of Functional Health Literacy in Adults (OR per 1 point increase=0.95, 95% CI 0.91-0.98)—were significantly associated with increased risk of mortality. These associations were almost unchanged when childhood cognitive ability was added to the model. When additionally adjusting for cognitive ability in older age, the health literacy-mortality associations were attenuated and no longer significant. Cognitive ability in older adulthood, but not childhood cognitive ability, accounted for most of the association between health literacy and mortality.

The genetic architecture of health literacy, cognitive ability, and health was examined in the fourth study. This study investigated whether polygenic profile scores for cognitive, education, and health-related traits were associated with performance on a test of health literacy using 5,783 ELSA participants. Greater odds of having adequate health literacy were associated with higher polygenic scores for better cognitive ability (OR per SD increase=1.34, 95% CI 1.26-1.42) and more years of schooling (OR=1.29, 95% CI 1.21-1.36). Reduced odds of having adequate health literacy were associated with higher polygenic scores for poorer self-rated health (OR=0.92, 95% CI 0.87-0.99) and schizophrenia (OR=0.91, 95% CI 0.85-

0.96). The association between health literacy, cognitive ability and health may, in part, be due to shared genetic influences.

This thesis provided an examination of the role of health literacy and cognitive ability in various aspects of health, including health behaviours, morbidity, and mortality. The findings suggest that that at least some of the associations between health literacy and health may be accounted for by cognitive ability, and that the association between health literacy and cognitive ability may be partly due to shared genetic aetiology. The degree of attenuation may depend on the health outcome used and the health literacy and cognitive ability measures used.

Lay summary

People who perform better on tests of planning, reasoning and solving problems—collectively referred to as cognitive ability—tend to have better health. Health literacy is thought to be the skills required to understand and use health information to make appropriate health decisions. People with better health literacy also tend to have better health. Cognitive ability and health literacy are also related, such that individuals who score higher on tests of health literacy also tend to score higher on tests of cognitive ability. This thesis investigated the associations of health literacy and cognitive ability, when studied together, with three aspects of health; smoking status, diabetes status, and risk of dying.

The first study found that individuals with higher health literacy and higher cognitive ability were less likely to report ever smoking. In individuals who reported ever smoking, those with higher health literacy and cognitive ability were more likely to have quit smoking. In the second study, higher scores on tests of health literacy and cognitive ability were associated with lower risk of reporting diabetes. The results of the first two studies suggest that higher scores on tests of health literacy and cognitive ability are associated with better health. In the third study, health literacy was not associated with risk of dying; however, higher cognitive ability was associated with lower risk of dying during an 8-year follow-up period. The results of the third study suggest that only lower cognitive ability, but not lower health literacy, is associated with an increased risk of dying.

The final study examined whether the associations between health literacy, cognitive ability and health may be because they share genetic influences. That is, the genes involved in health literacy, cognitive ability and health may overlap. This study found that individuals with more of the genes associated with higher cognitive

ability and staying in education longer, had higher health literacy tests scores. Conversely, those with more of the genes associated with increased risk of schizophrenia and increased risk of self-reported poor health had lower health literacy test scores. Overall, the results of this thesis provide additional support that health literacy, cognitive ability and health are strongly related, and the relationship may be partly due to shared genetic influences.

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The analyses in this thesis were only possible because of the availability of data from large and well characterised cohort studies. I would like to thank the participants of the Lothian Birth Cohort 1936 (LBC1936) and the English Longitudinal Study of Ageing (ELSA). I would also like to thank the LBC1936 and ELSA research teams for making their valuable datasets available.

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1. Health literacy

Successfully functioning in the healthcare system is a complex task (Nielsen-Bohlman, Panzer, & Kindig, 2004). Patients are required to effectively communicate any health concerns to healthcare professionals, comprehend and evaluate health information, and make decisions based on this information. Health services often rely on written materials to inform and educate patients. Patients are expected to read and understand these written materials, such as information leaflets, consent forms, and drug labels. These health materials, however, are often written at a level exceeding the reading skills of many of individuals for whom the information was designed (Rudd, Moeykens, & Colton, 2000). Healthcare systems are becoming ever more complex in the UK and elsewhere because of government policy stressing patient participation and promoting informed patient decision-making (Protheroe, Nutbeam, & Rowlands, 2009). Patients are expected to fully understand all healthcare options available to them and have the capacity to make informed decisions regarding these care options.

Health literacy, a term first introduced in the 1970s (Simonds, 1974), is a composite term for the skills needed to function effectively in the healthcare environment (Berkman, Sheridan, Donahue, Halpern, & Crotty, 2011). Health literacy is thought to include basic literacy skills such as reading, writing and numeracy, as well as health-related knowledge and the ability to verbally communicate about health (oral literacy). These capabilities are essential for reading written health documents, such as health information leaflets and medicine labels (Berkman et al., 2011; Bostock & Steptoe, 2012). Individuals who lack these basic skills will be severely disadvantaged in a healthcare environment that relies heavily on written materials. Low health literacy has been identified as a risk factor for poor health (Nutbeam, 2000). In fact, health literacy has been found to be a better predictor of health status than age, income, employment, race/ethnicity and education (Ad Hoc Committee on Health Literacy for the Council on Scientific Affairs & American Medical Association, 1999).

The prevalence of limited health literacy is high. A systematic review of 85 studies carried out in the US including over 30,000 participants found that 26% of participants had low health literacy and a further 20% had marginal health literacy (Paasche-Orlow, Parker, Gazmararian, Nielsen-Bohlman, & Rudd, 2005). A study carried out using participants based in 8 European counties similarly found that nearly 50% of the samples investigated had limited health literacy (Sørensen et al., 2015). Limited health literacy levels tend to be higher in populations who rely most heavily on healthcare services. Limited health literacy is more common in older adults, those with lower education, lower socioeconomic status and poorer health status (Baker, Gazmararian, Sudano, & Patterson, 2000; Kobayashi, Wardle, Wolf, & von Wagner, 2016a; Nielsen-Bohlman et al., 2004; Sørensen et al., 2015). Such high prevalence of limited health literacy has been coined a “silent epidemic” by the Institute of Medicine (Parker, Wolf, & Kirsch, 2008; Parker & Ratzan, 2010).

1.1. Defining health literacy

Many different definitions of health literacy have been proposed. Whereas researchers agree that health literacy is multifaceted and describes the general set of capabilities needed to meet the demands of healthcare, there is disagreement as to the exact skills and abilities involved in this construct (Sørensen et al., 2012). Narrow definitions emphasise health-related reading, writing and numeracy skills required to be able to adequately comprehend written health materials (Sørensen et al., 2012).

A distinction has been made regarding the view of health literacy from a clinical and public health perspective (Guzys, Kenny, Dickson-Swift, & Threlkeld, 2015). From the clinical perspective, definitions of health literacy focus on the skills and abilities of the individual to find and interpret health information (Baker, 2006; Guzys et al., 2015; Nutbeam, 2008). According to the clinical perspective, health literacy is seen as relatively stable over time (Baker, 2006; Berkman, Davis, & McCormack, 2010). The most commonly used definition of health literacy, which has been adopted by the Institute of Medicine, posits that health literacy is “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions” (Nielsen-Bohlman et al., 2004; Ratzan & Parker, 2000). This clinical definition emphasises the skills of the individual and establishes health literacy as a risk factor for poor health (Nutbeam, 2008).

Definitions of health literacy deriving from a public health perspective provide much broader definitions that emphasise the skills and knowledge required to manage all aspects of health including everyday health promotion and preventing future ill-health (Guzys et al., 2015; Sørensen et al., 2012). Taking a public health approach, Nutbeam (2000) characterised health literacy as the “personal, cognitive and social skills” needed to “maintain good health”. According to this view, health literacy is seen as more “dynamic” (Berkman et al., 2010). Health literacy is seen as an asset, rather than a risk factor (when low), and through education and health promotional programs, health literacy can be improved (Nutbeam, 2008).

In a bid to expand the definition of health literacy beyond the ability to apply basic literacy skills to written health materials, Nutbeam (2000) proposed three different types of health literacy (Al Sayah, Majumdar, Williams, Robertson, & Johnson, 2013; Nutbeam, 2000):

Functional health literacy: The necessary reading and writing skills required to understand written health documents. This is similar to the narrow definitions of health literacy.

Interactive health literacy: The more advanced cognitive skills that, alongside social skills, can be utilised to actively take part in healthcare activities. This type of health literacy recognises that communication is a necessary component for effectively functioning in healthcare. Interactive health literacy is the ability to comprehend and apply the health information obtained through a variety of different types of communication.

Critical health literacy: Even more advanced cognitive skills that are used to critically analyse health information and make informed decisions based on this evaluation.

Sørensen et al. (2012) systematically reviewed the existing definitions of health literacy and identified 17 distinct definitions. Following this review, and following a content analysis of these definitions, Sørensen et al. (2012) proposed the following, all-encompassing, definition of health literacy:

> Health literacy is linked to literacy and entails people's knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course (Sørensen et al., 2012, p. 3) .

This all-encompassing definition of health literacy has been adopted by the World Health Organisation (World Health Organisation, 2013).

1.2. Theories of health literacy

Just as there are numerous definitions of health literacy, numerous theoretical models of health literacy have been proposed. In their systematic review, Sørensen et al. (2012) reviewed the various conceptual models of health literacy. Most models document the sociodemographic antecedents of low health literacy. Older age, being from an ethnic minority group, lower education and a lower occupational social class have been identified as being important contributors to low health literacy (Sørensen et al., 2012). Many models also recognise functional abilities such as cognitive ability, including memory and reasoning, as being important precursors to health literacy (Sørensen et al., 2012). Most also acknowledge that external, system-level factors, such as the complexity of the healthcare system, influence health literacy. Whereas a variety of different definitions and theories of health literacy have been proposed, what they all have in common is that health literacy is assumed to be the set of competencies required to understand and use health information. These competencies can be called upon to help with the effective management of one's health and effective decision-making within the healthcare environment (Sørensen et al., 2012).

Some models theorise the pathway between health literacy and health outcomes. These models tend to assume that health literacy is not directly associated with health. Instead health literacy has indirect associations with health by increasing, for example, health knowledge, which in turn, is associated with health outcomes (Baker, 2006; Paasche-Orlow & Wolf, 2007). Two models which describe the association between health literacy and health outcomes—Baker's (2006) conceptual model of the association between individual capacity, health literacy and health, and Paasche-Orlow and Wolf's (2007) model of the causal pathways between health literacy and health outcomes—will be described in sections 1.2.1 and 1.2.2, below.

1.2.1. Baker's (2006) conceptual model of the association between individual capacity, health literacy and health outcomes

A illustration of Baker's (2006) model is shown in Figure 1.1. This model was developed to document the different domains of health literacy and to account for the relationship between health literacy and health outcomes (Baker, 2006). There are two major domains in this model. The first is individual capacity. Individual capacity refers to the capabilities that are fundamental for functioning within the healthcare system (Baker, 2006). Baker (2006) identified two sets of individual capacities; reading fluency—the ability to read and understand health information—and prior knowledge of health-related words (e.g., vocabulary) and prior knowledge and experience of the healthcare system.

Individual capacity (e.g., reading skills and prior health knowledge) enable individuals to develop better health literacy—the second domain of Baker's model. Baker (2006) divided health literacy into health-related print and oral literacy; the ability to understand written and spoken health information, respectively. However, Baker (2006) acknowledged that it is not known whether print and oral health literacy are separate constructs or whether they form part on the same underlying ability. In line with some of the definitions of health literacy detailed in Section 1.1, Baker (2006) recognised that health literacy is not only characterised by features of the individual (e.g., reading fluency and prior knowledge), but that external factors relating to, for example, the complexity of the information encountered in the healthcare system, also play a role in determining a person's level of health literacy.

In turn, health literacy, along with many other factors (e.g., culture and norms), leads to acquisition of new health knowledge, greater self-efficacy of health, and health behavioural changes, and these subsequently lead to better health outcomes (Baker, 2006).

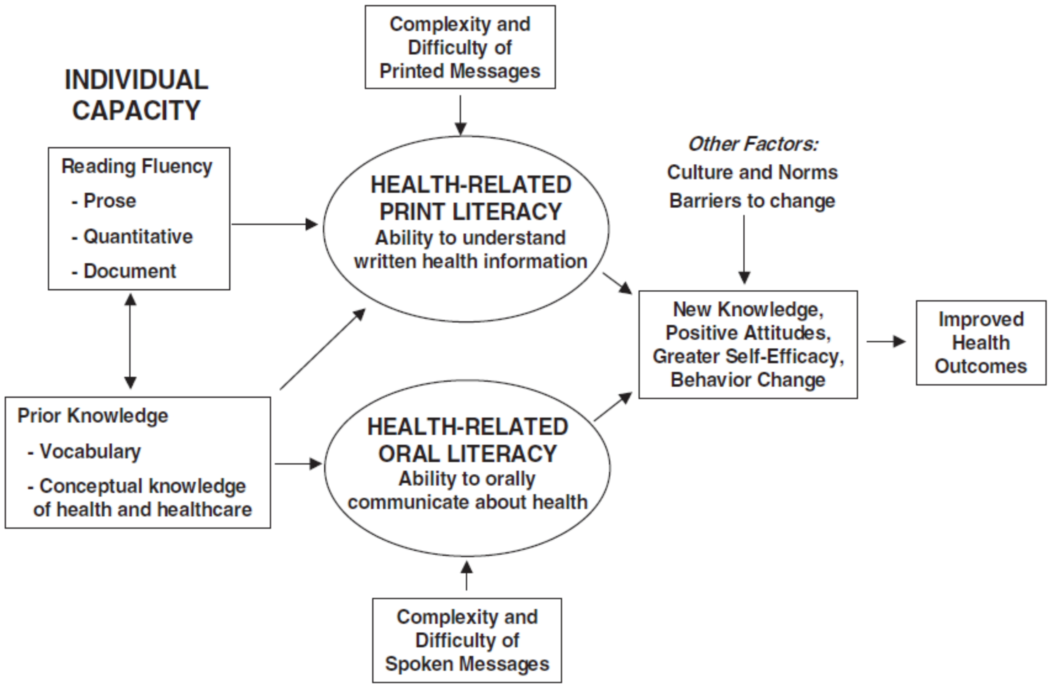

Figure 1.1. A schematic diagram of Baker's (2006) conceptual model of the association between individual capacity, health literacy and health. Reprinted with permission from Baker (2006).

1.2.2. Paasche-Orlow and Wolf's (2007) model of the causal pathways between limited health literacy and health outcomes

A similar, though more detailed, model developed to better understand the association between health literacy and health outcomes was proposed by Paasche-Orlow and Wolf (2007) and an illustration of this model is shown in Figure 1.2. In this model, demographic, socioeconomic, cognitive and functional factors are thought to be prerequisites for health literacy. This model assumes that health literacy does not directly determine health outcomes, but likely works through three types of health actions (Osborn, Paasche-Orlow, Bailey, & Wolf, 2011; Paasche-Orlow & Wolf, 2007; von Wagner, Steptoe, Wolf, & Wardle, 2009). These three health actions are:

1. *Access and utilisation of healthcare:* Individuals with limited health literacy may be less able to navigate through healthcare and may not use available health services as much as those with adequate health literacy (Paasche-Orlow & Wolf, 2007; von Wagner et al., 2009).
2. *Provider-patient interaction:* Individuals with limited health literacy may know less about health and this may impact on their ability to understand healthcare providers discussing their health and therefore those with limited health literacy may not be able to make informed decisions about their health (Paasche-Orlow & Wolf, 2007).
3. *Self-care:* Those with limited health literacy may have lower knowledge of their disease and therefore be less able to self-manage their disease (Paasche-Orlow & Wolf, 2007).

For all three health actions, Paasche-Orlow and Wolf (2007) recognised that it is not only individual capabilities that affect the association between health literacy and health outcomes, but that external factors related to the healthcare system are also important. For example, externals factors such as the complexity of the environment to be navigated (access and utilisation of healthcare in Figure 1.2), the communication skills of the healthcare professional (provider-patient interaction), and the available technologies for managing self-care all play a role in determining health outcomes.

Both Baker's (2006) model and Paasche-Orlow and Wolf's (2007) model were designed to understand why lower health literacy is associated with poor health. A review of the empirical evidence for an association between health literacy and health outcomes will be reviewed in Section 1.4. First, Section 1.3 will provide a description of how health literacy is measured in research.

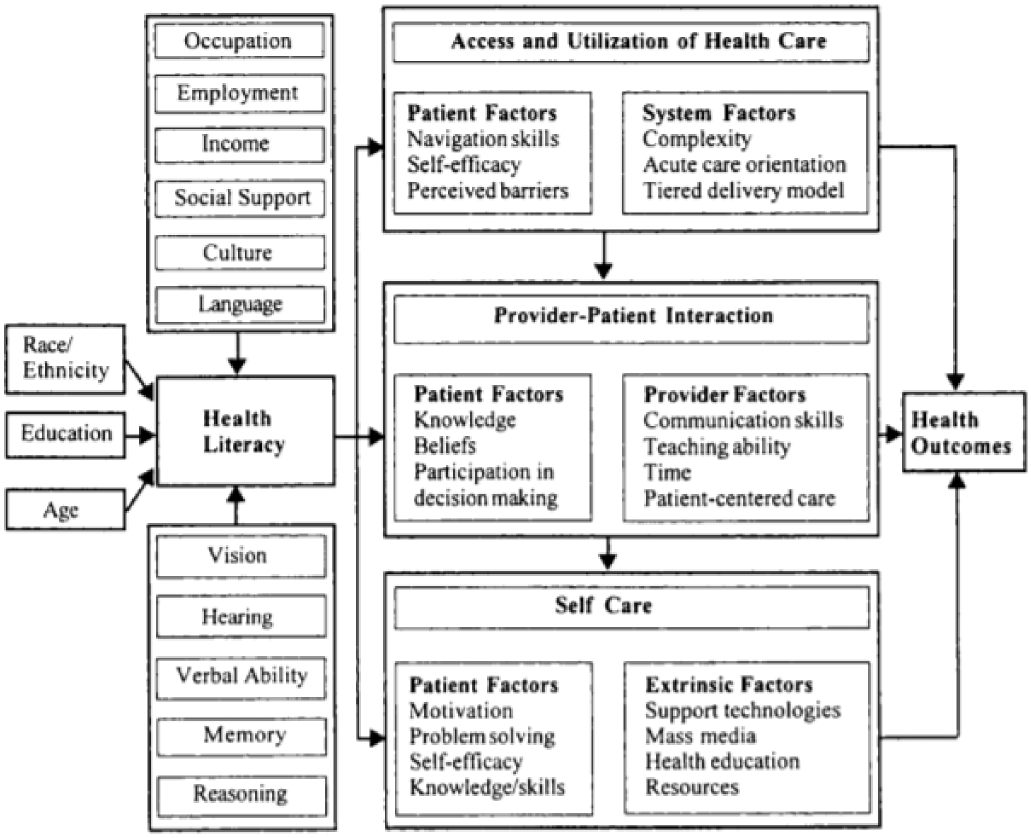

Figure 1.2. A schematic of Paasche-Orlow and Wolf's (2007) model of the causal pathways linking limited health literacy to health outcomes. Permission granted by PNG Publications to reprint figure. Paasche-Orlow, M. K., & Wolf, M. S. (2007). The causal pathways linking health literacy to health outcomes. *American Journal of Health Behavior,* 31 Suppl 1, S19-26. doi: 10.5555/ajhb.2007.31.supp.S19

1.3. Measuring health literacy

Numerous tests of health literacy have been developed. Some are designed for use in clinical settings and therefore are necessarily brief and easy to administer. These clinical measures are often designed as screening tools to categorise individuals into those with limited or adequate health literacy (Sørensen et al., 2013). Others are designed to be comprehensive assessments of health literacy and cover a much broader set of skills and are therefore lengthy to administer. Some assess objective performance on health-related tasks, others are subjective scales. Below, I will describe some of the most commonly used assessments of health literacy.

1.3.1. Test of Functional Health Literacy in Adults

The Test of Functional Health Literacy in Adults (TOFHLA; Baker, Williams, Parker, Gazmararian, & Nurss, 1999; Parker, Baker, Williams, & Nurss, 1995) assesses health-related reading and numeracy skills (functional health literacy) , using materials that were designed to be like those patients would encounter in a health setting, such as a consent form (Baker et al., 1999). This test consists of two sections; a reading comprehension section and a numeracy section. The reading comprehension section consists of three health-related passages in which every 5th to 7th word is missing. The participant is to decide, from a list of 4 words, which is the missing word. There are 50 items in the reading comprehension section. The numeracy section consists of 17 items assessing health-related numeracy skills. Participants are given mock health materials to read, such as a medicine label. An example of types of materials provided to participants is shown in Figure 1.3. Participants are then orally asked questions about the information provided on these health materials (Parker et al., 1995). The score on the 17-item numeracy test is weighted such that the maximum score on this section is 50 and the total maximum score is 100. Scores are often categorised as inadequate (0-59 points), marginal (60-74 points) and adequate (75-100 points) health literacy. This test is often classed as the "gold standard" health literacy assessment (Mancuso, 2009).

The original TOFHLA took approximately 22 minutes to administer. Baker et al. (1999) developed a shortened form of the TOFHLA (S-TOFHLA) which reduced the testing time to 12 minutes. In this shortened version, the reading comprehension section consisted of two passages with 36 items and the numeracy section consisted of 4 items. Each reading comprehension item was assigned a score of 2 points for a correct answer, and each of the numeracy items was assigned a score of 7 points, thus the test has a total score of 100. Like the original TOFHLA, scores were divided into inadequate (0-53 points), marginal (54-66 points) and adequate (67-100 points) health literacy (Baker et al., 1999).

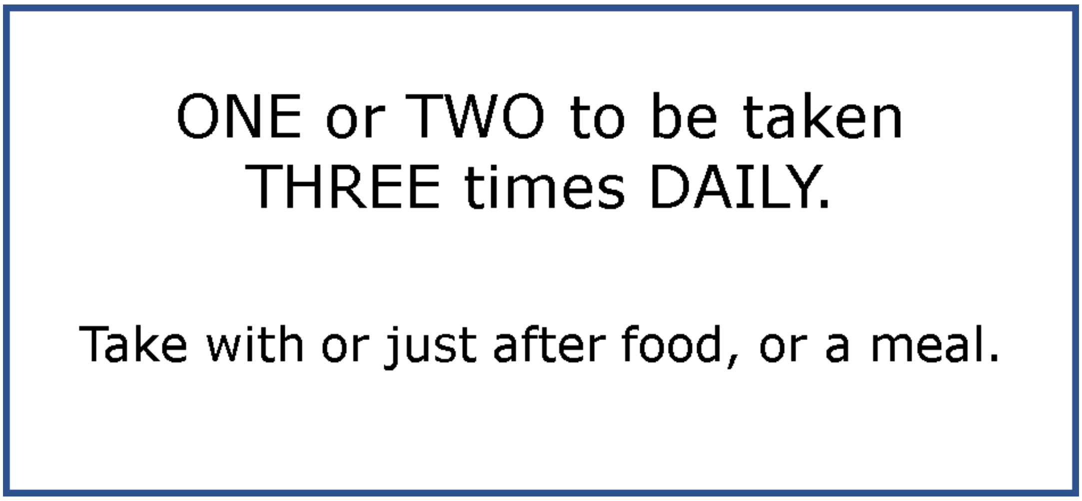

Figure 1.3. Example of the types of materials used in the Test of Functional Health Literacy in Adults, and other tests of functional health literacy.

The TOFHLA and S-TOFHLA have been found to have reasonably good psychometric properties. The TOFHLA has been found to correlate highly with other, non-health-related, measures of reading comprehension, such as the Revised Wide

Range Achievement Test (*r* = 0.84; Parker et al., 1995) . The internal reliability of the S-TOFHLA reading comprehension section is high (Cronbach's α = 0.97; Baker et al., 1999) ; however, the internal consistency is lower for the shorter numeracy section (Cronbach's α = 0.68; Baker et al., 1999) .

1.3.2. Rapid Estimate of Adult Literacy in Medicine

Another popular assessment of health literacy is the Rapid Estimate of Adult Literacy in Medicine (REALM; Davis et al., 1991; Davis et al., 1993) .This test assesses the ability to recognise and pronounce medical words (Davis et al., 1991; Davis et al., 1993; Nielsen-Bohlman et al., 2004). Participants are provided with a piece of paper containing lists of medical words and they are asked to read these words aloud. The words chosen for this test were identified using written health materials that were commonly given to patients. The words start of easy (e.g., "fat", and "pill"), and become progressively harder (e.g., "osteoporosis" and "impetigo"). It is assumed that if an individual is unable to pronounce a health-related word, they will have difficulties reading and understanding health materials containing these words (Nielsen-Bohlman et al., 2004). The original version of this test required participants to read aloud a list of 125 health-related words (Davis et al., 1991). A shortened version was subsequently developed containing 66 health-related words (Davis et al., 1993), and it is this shortened version has been used frequently in the literature. In line with the literature, throughout this thesis the term "REALM" will be used to refer to the 66-item version of this test. One point is awarded for each correctly pronounced word. Scores on the (66-item) REALM are often divided into four reading grade levels: 3rd grade and below (0-18 points), 4th to 6th grade (19-44 points), 7th to 8th grade (45-60 points), and 9th grade and above (61-66 points; Davis et al., 1993) .

The popularity of the REALM owes largely to its short, less than 3-minute, administration time. Despite its short administration time, even shorter versions have been developed including a 7-item version—the REALM Short-Form (REALM-SF; Arozullah et al., 2007) —and an 8-item version—the REALM Revised (REALM-R; Bass, Wilson, & Griffith, 2003) .

Measures of test-retest reliability (*r* = 0.99; Davis et al., 1993) and internal consistency (Cronbach's α = 0.98; Dumenci, Matsuyama, Kuhn, Perera, & Siminoff, 2013) are very high for the REALM. The Spearman rank-order correlation between S-TOFHLA and REALM was found to be 0.80 in the original S-TOFHLA paper (Baker et al., 1999). However, other studies have found lower correlations between these tests (*rho* = 0.46; Murray, Johnson, Wolf, & Deary, 2011) .

1.3.3. Newest Vital Sign

Though not as widely used as the REALM and S-TOFHLA, another popular screening tool for health literacy is the Newest Vital Sign (Weiss et al., 2005). Like the S-TOFHLA, the Newest Vital Sign assesses health-related reading comprehension and numeracy skills (Weiss et al., 2005). This brief, 5-minute, 6-item test requires participants to read a nutrition label for a container of ice cream and answer six questions about the information provided on this label (Weiss et al., 2005). An example of the type of nutrition label provided to participants during this test is provided in Figure 1.4. Most of the questions require participants to carry out mental calculations based on the numbers provided on the label. Internal reliability (Cronbach's α = 0.76; Weiss et al., 2005) and concurrent validity (correlation with the TOFHLA *r* = 0.59; Weiss et al., 2005) have been found to be reasonable for the Newest Vital Sign.

Nutrition Information		
TYPICAL VALUES		
	Per 100g	Per serving (20g)
Energy (kJ)	**2194**	**439**
(kcal)	**526**	**105**
Fat (g)	**32.5**	**6.5**
of which saturates (g)	2.3	0.5
of which monounsaturates (g)	25.2	5.0
of which polyunsaturates (g)	5.0	1.0
Carbohydrates (g)	**51.5**	**10.3**
of which sugars	0.4	0.1
Fibre (g)	**5.2**	**1.0**
Protein (g)	**5.9**	**1.2**
Salt (g)	**1.6**	**0.3**

Figure 1.4. An example of the kind of nutrition label provided to participants during the Newest Vital Sign

1.3.4. Other health literacy measures

The S-TOFHLA, REALM, and to a lesser extent, the Newest Vital Sign, are the most widely used tests of health literacy. These assessments are popular because they are relatively easy to administer, and they are brief. However, these brief measures have been criticised because they only measure functional health literacy; that is, mostly health-related reading and numeracy skills (I. M. Bennett, Chen, Soroui, &

White, 2009; Nielsen-Bohlman et al., 2004). Whereas tests such as the S-TOFHLA and the REALM have been found to have good psychometric properties, reviews of the content of these tests question their usefulness given that they assess only a small number of components of the multidimensional construct of health literacy (Dumenci et al., 2013; Jordan, Osborne, & Buchbinder, 2011).

The Comprehensive Health Activities Scale (CHAS) was developed to overcome the limitations of these brief functional health literacy tests (Curtis et al., 2015). For the CHAS, the authors selected nine common but cognitively challenging health-related tasks that older adults would be expected to undertake in a healthcare setting. Like the S-TOFHLA and Newest Vital Sign, the CHAS assessed comprehension of printed materials and health-related numeracy skills. For example, in one task participants were required to read a consent form for a medical procedure and answer questions on it; another required participants to calculate and interpret blood sugar levels. Unlike the S-TOFHLA and Newest Vital Sign, the CHAS also assessed comprehension of spoken communication. One task involved the tester reading aloud instructions for a course of medication, and another required participants to watch a video clip explaining how to manage asthma symptoms. Participants were then asked questions about the information they just heard to assess verbal comprehension of health information. Despite the CHAS assessing a broader set of skills than that measured using the S-TOFHLA, REALM, and Newest Vital Sign, the authors question whether this lengthy 60-minute test provides any additional information about health literacy above that provided by brief tests of functional health literacy (Curtis et al., 2015). The authors (Curtis et al., 2015) found that the CHAS correlated very highly with the TOFHLA (r = 0.81), and relatively highly with the Newest Vital Sign (r = 0.75), and REALM (r = 0.68). Although the CHAS assesses a broader set of health-related skills than brief tests of functional health literacy, all test items in the CHAS loaded on only one general latent trait (Curtis et al., 2015). Therefore, all the items in the CHAS are assessing the same underlying ability. Brief tests of functional health literacy, such as the S-TOFHLA, REALM, and Newest Vital Sign will likely be measuring this same underlying construct (Curtis et al., 2015).

Other comprehensive measures of health literacy have assessed subjective health literacy using self-report questionnaires. For example, the Health Literacy Questionnaire (HLQ) is a 44-item scale that assesses functional, interactive and critical health literacy (Osborne, Batterham, Elsworth, Hawkins, & Buchbinder, 2013). The European Health Literacy Survey Questionnaire (HLS-EU-Q) is a 47-item questionnaire designed to capture a broader concept of health literacy (Sørensen et al., 2013). This questionnaire assesses the competencies to access, understand, appraise, and apply health information in healthcare, disease prevention, and health promoting settings (Sørensen et al., 2013). The HLS-EU-Q was designed for use in general samples and can take up to 30 minutes to administer. Examples of some of the questions in the HLS-EU-Q include participants self-reporting how easy it is for them to (Sørensen et al., 2013):

- understand what the doctor says to them,
- judge how reliable health warnings are,
- and decide if they should have a flu vaccination.

At the other extreme, very brief self-reported measures of health literacy have been developed. Even short assessments such as the REALM and the Newest Vital Sign, which take less than 5 minutes to administer, can be viewed as too lengthy for use in some busy clinical settings (Chew et al., 2008). To overcome this, some studies have assessed health literacy by asking between one and three subjective questions about participant’s ability to complete some basic health-related tasks

(Chew et al., 2008). One question—"How confident are you filling out forms by yourself?"—has been found to be a good indicator of adequate health literacy (Chew et al., 2008).

Despite criticisms of them (Dumenci et al., 2013; Jordan et al., 2011), and the availability of more detailed health literacy tests, tests of functional health literacy including the TOFHLA, S-TOFHLA, REALM and Newest Vital Sign remain the most frequently used measures of health literacy. I note that the empirical work reported in this thesis uses the S-TOFHLA, REALM, and Newest Vital Sign. It also uses a brief 4-item test of functional health literacy (described in more detail in Section 1.4.2) designed to assess health-related reading comprehension skills (Bostock & Steptoe, 2012; Thorn, 2009). This thesis does not utilise more detailed health literacy measures designed to assess a broader conceptualisation of health literacy.

A wealth of research has been carried out investigating whether limited health literacy, assessed with these popular tests of functional health literacy, is associated with poor health (Berkman et al., 2011; Dewalt, Berkman, Sheridan, Lohr, & Pignone, 2004). In Section 1.4 I will provide a review of the evidence linking limited health literacy to poor health outcomes, as well as other aspects of health, such as health behaviours and use of health services.

1.4. Health literacy and health

Being a patient is a complex task (Gottfredson, 2004). Adequate health literacy—that is, adequate health-related skills and knowledge—may be a prerequisite to good health (Baker, 2006; Paasche-Orlow & Wolf, 2007). For two decades, researchers have been investigating the association between health literacy and poor health and have found that limited health literacy is associated with a whole range of health-related outcomes, including taking medication incorrectly, using preventative health services less frequently, greater hospitalisation, greater use of emergency health services, poorer global health status and greater risk of death (Berkman et al., 2011; Dewalt et al., 2004).

Associations between health literacy and both physical and mental health have been identified (Adams et al., 2009; Berkman et al., 2011; Wolf, Davis, et al., 2005). Wolf, Gazmararian, and Baker (2005) investigated the association between health literacy, measured by the S-TOFHLA, and a range of measures of general health status in a cross-sectional study of nearly 3,000 older adults in the US. They found that individuals with inadequate health literacy, compared to those with adequate health literacy, had significantly lower self-reported physical (β = -0.6, 95% CI -8.4 to -3.5) and mental (β = -4.9; 95% CI -6.7 to -3.1) functioning, assessed using the 36-Item Short-form Health Survey, even when adjusting for a range of sociodemographic variables and health risk behaviours (Wolf, Gazmararian, et al., 2005). When compared to those with adequate health literacy, those with inadequate health literacy were more likely to report limitations in activities of daily living (ADLs; OR = 2.83; 95% CI 1.62 to 4.96), and limitations in instrumental activities of daily living (IADLS; OR = 2.25, 95% CI 1.74 to 2.92), after adjusting for sociodemographic variables and health behaviours (Wolf, Gazmararian, et al., 2005).

Whereas Wolf, Gazmararian, et al. (2005) found an association between health literacy and mental health status, not all studies have found consistent results when examining the role of health literacy and mental health. Using the same sample of older adults, Gazmararian, Baker, Parker, and Blazer (2000) examined whether health literacy was associated with depressive symptoms. When adjusting for sociodemographic variables, measures of social support and health behaviours, those with inadequate health literacy had increased odds of being depressed (OR = 1.7, 95% CI 1.2 to 2.2), assessed using the Geriatric Depression Scale, compared to participants with adequate health literacy. However, when additionally adjusting for physical health status (ADLs, IADLS, and self-reported health), this association was attenuated and non-significant (OR = 1.2, 95% CI 0.9 to 1.7).

1.4.1. Health literacy and chronic disease

Chronic disease is common. In the UK, 60% of the adult population have at least one chronic disease, and this percentage rises to 75% in those aged over 75 (Shaw, Ibrahim, Reid, Ussher, & Rowlands, 2009). Managing chronic disease, such as diabetes or hypertension, is complex. For example, patients must make changes to their behaviour (e.g., eating well and exercising), they may have to follow complicated medication regimes, and know when to seek help from health professionals. Following a diagnosis of a chronic condition, patients are expected to be proactive and learn about their condition. For conditions such as diabetes, patients must monitor their symptoms and adapt their behaviour accordingly (Schillinger et al., 2002). Individuals with limited health literacy may not have the skills and knowledge needed to successfully manage chronic disease.

Few studies have examined the association between health literacy and prevalence of chronic diseases. One cross-sectional study (Wolf, Gazmararian, et al., 2005) found that individuals with inadequate health literacy were 48% (OR = 1.48, 95% CI 1.09 to 2.02) more likely to report a diagnosis of diabetes, and 69% (OR = 1.69, 95% CI 1.02 to 2.80) more likely to report a diagnosis of heart failure compared to those with limited health literacy, when also adjusting for sociodemographic variables, and health behaviours. When controlling for the same covariates, rates of hypertension, coronary artery disease, bronchitis or emphysema, asthma, arthritis, and cancer were similar for individuals with adequate, marginal and inadequate health literacy (Wolf, Gazmararian, et al., 2005). Another cross-sectional study (Adams et al., 2009) reported that when compared to participants who scored ≥4 on the Newest Vital Sign, individuals who scored 3 or less were more likely to report having diabetes (OR = 1.9, 95% CI 1.4 to 2.6), and having had a heart attack/angina (OR = 2.2, 95% CI 1.4 to 3.3), or a stroke (OR = 3.9, 95% CI 1.7 to 9.0), when adjusting for age, sex, income and education. Reporting hypertension, asthma, arthritis, cancer and depression were not associated with scores on the Newest Vital Sign (Adams et al., 2009). A systematic review (Berkman et al., 2011) reported that there was insufficient evidence linking health literacy to chronic disease.

A wealth of research has been conducted examining the association between health literacy and knowledge of chronic disease. In chronic disease patients, low health literacy has consistently been found to be associated with lower knowledge of chronic disease, including knowledge of heart failure (Gazmararian, Williams, Peel, & Baker, 2003; Macabasco-O'Connell et al., 2011), hypertension (Gazmararian et al., 2003; Williams, Baker, Parker, & Nurss, 1998), asthma (Gazmararian et al., 2003; Williams, Baker, Honig, Lee, & Nowlan, 1998), HIV (Wolf, Davis, et al., 2005), and diabetes (Bains & Egede, 2011; Caruso et al., 2018; Marciano, Camerini, & Schulz, 2019; Powell, Hill, & Clancy, 2007). These findings are consistent with the conceptual models proposed by Paasche-Orlow and Wolf (2007) and Baker (2006), which suggest that higher health literacy leads to increased health-related knowledge.

The evidence for an association between health literacy and chronic disease management skills and disease control are mixed. The association between health literacy and HbA1c levels—an indicator of poor glycaemic control—has been investigated in patient with diabetes. Whereas, some studies have found that lower health literacy predicted increased HbA1c levels (Lamar et al., 2019; Schillinger et al., 2002; Tang, Pang, Chan, Yeung, & Yeung, 2008) others have not (Bains & Egede, 2011; Williams, Baker, Parker, et al., 1998). A recent systematic review and meta-analysis of 36 studies comprising 12,293 participants with type 1 or type 2 diabetes (Marciano et al., 2019) found a small but significant association between higher health literacy and lower HbA1c levels (r = -0.048, p = .027) . In subgroup analyses, the effect for an association between higher health literacy and lower HbA1c levels was only seen in studies using objective tests of health literacy (n = 8,443, number of studies = 24, r = -0.046, p = .034) and not in studies using subjective tests (n = 3,850, number of studies = 12, r = -0.037, p = .439; Marciano et al., 2019).

1.4.2. Health literacy and mortality

Whereas there is mixed evidence of an association between health literacy and morbidity, there is good evidence for an association between health literacy and mortality (Baker et al., 2007; Berkman et al., 2011; Bostock & Steptoe, 2012; Cavanaugh et al., 2010; Sudore et al., 2006). Baker et al. (2007) tested whether health literacy scores predicted mortality in 3,260 adults aged over 65 years in the US who were then followed up for 6 years. Health literacy was assessed using the S-TOFHLA and participants were categorised as having adequate, marginal or inadequate health literacy. When adjusting for age and measures of health status (including self-reported physical and mental health, and chronic conditions), individuals with inadequate health literacy had a 52% increased risk of dying (HR = 1.52, 95% CI 1.26 to 1.83), compared to those with adequate health literacy. The size of this association did not change when health behaviours were added to the model, or when individuals with a possible cognitive impairment, defined as a score of less than or equal to 18 on the Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975) , were removed. This study then tested whether health literacy was associated with specific causes of death. This study examined cardiovascular, cancer, and other deaths. After controlling for demographic variables, inadequate health literacy (HR = 1.52; 95% CI 1.16 to 2.00) and marginal health literacy (HR = 1.39; 95% CI 1.02 to 1.90) were associated with increased risk of cardiovascular mortality, compared to individuals with adequate health literacy (Baker et al., 2007).

Using participants in the English Longitudinal Study of Ageing (ELSA), a sample of middle-aged and older English adults, Bostock and Steptoe (2012) tested whether an association between heath literacy and mortality was independent of other established risk factors for death, such as age, sociodemographic variables, ill-health, health behaviours and cognitive ability. In ELSA, health literacy was assessed with a validated, four-item test of health-related reading comprehension that has previously been used in the International Adult Literacy Survey and the Adult Literacy and Life Skills Survey (Thorn, 2009). Participants were provided with a mock label for a packet of over-the-counter medication (similar to that shown in Figure 1.3), and they were then asked four questions about the information provided on this label (for example, "what is the maximum number of days you may take the medication?"). One point was awarded for each correctly answered question (maximum score = 4). I note that the ELSA sample, and this four-item test of health literacy are used in three of the empirical chapters in this thesis. In their analysis of the association between health literacy and mortality, Bostock and Steptoe (2012) split health literacy scores into three categories: high (all questions correct), medium (1 error) and low (greater than 1 error). A total of 8,316 participants were followed-up for a mean of 5.3 years. Adjusting for sociodemographic measures, low health literacy was associated with a 57% increase in all-cause mortality (HR = 1.57, 95% CI 1.29 to 1.92). The association was reduced after adjusting for health status and health behaviours, however health literacy still predicted mortality (HR = 1.41; 95% CI 1.15 to 1.73). Adding tests of cognitive function (orientation in time, immediate recall of words, and animal naming) further attenuated this association; however, low health literacy was still significantly associated with increased risk of all-cause mortality (HR = 1.26; 95% CI 1.03 to 1.56; Bostock & Steptoe, 2012).

1.4.3. Health literacy and health behaviours

Theories linking health literacy to health outcomes tend not to assume that health literacy is directly associated with health outcomes, but instead, these theories posit that health literacy is associated with health by a possible path through, for example, knowledge and self-care (Baker, 2006; Paasche-Orlow & Wolf, 2007). Individuals with lower health literacy may have difficulties understanding the health benefits of, for example, eating a healthy diet, taking part in regular physical activity, and not smoking, and therefore may be less likely to take part in health promoting behaviours.

The evidence for an association between health literacy and participating in health promoting behaviours is mixed (Fernandez, Larson, & Zikmund-Fisher, 2016; von Wagner, Knight, Steptoe, & Wardle, 2007; Wolf, Gazmararian, & Baker, 2007). In a sample of UK participants, von Wagner et al. (2007) tested whether health literacy, measured with a UK version of the TOFHLA, was associated with a range of different health behaviours (eating at least 5 portions of fruit and vegetables a day, exercising in the last 7 days, and not smoking). Adjusting for age, sex, ethnicity, language (whether or not English is first language), education and income, von Wagner et al. (2007) found that a one-point increase (score 0-100) on the TOFHLA was associated with increased rates of eating at least 5 portions of fruit and vegetables a day (OR = 1.02, 95% CI 1.003 to 1.03) and not smoking (OR = 1.02, 95% CI 1.003 to 1.03), but not with exercising in the last 7 days. A similar study was carried out using community-dwelling older adults in the US (Wolf et al., 2007). This study tested the association between health literacy, measured using the S-TOFHLA, and four health behaviours: smoking, alcohol consumption, physical activity, and body mass index. Despite the fact the US and UK studies used versions of the TOFHLA, and despite the fact they controlled for a similar set of covariates, the US study found that health literacy was not associated with any of the health behaviours examined (Wolf et al., 2007). Because of these inconsistent results, a systematic review of the association between health literacy and health outcomes (Berkman et al., 2011) concluded that there was insufficient evidence for an association between health literacy and health behaviours.

1.4.4. Health literacy and use of health services

Self-managing health not only involves taking part in health-promoting behaviours, it also involves being able use healthcare services effectively and efficiently (Baker, Parker, Williams, & Clark, 1998; World Health Organisation, 2013). Individuals with limited health literacy may not have the skills to know when to seek advice from healthcare professionals. When they do seek help, they may not be able to understand and follow any advice provided. This section will review the literature investigating the association between health literacy and use of health services.

1.4.4.1. Adherence to medication

There is some evidence that individuals with lower health literacy are less likely to adhere to medication or are less likely to take prescribed medication correctly. A meta-analysis (Zhang, Terry, & McHorney, 2014) of 11,121 participants found a small but significant association between health literacy and medication adherence (unweighted $r = 0.081$, weighted $r = 0.056$, $p < .001$). A systematic review (Berkman et al., 2011) found insufficient evidence for an association between health literacy and adherence to medication regimens, due to inconsistent results; however, they also reported moderate evidence that low heath literacy is associated with poorer skills in taking medication correctly (Berkman et al., 2011) and with poorer comprehension of written health information, such as medicine labels, and health messages (Berkman et al., 2011).

1.4.4.2. Use of preventative services

There is mixed evidence for an association between health literacy and use of preventative screening services. Fernandez et al. (2016) found that subjective health literacy, assessed with a single question about confidence filling in medical forms, was associated with increased mammography screening in women (OR = 2.22, 95% CI 1.21 to 4.66), but was not associated with flu immunization, cholesterol testing, self-breast examination or prostate examination in a sample of middle-aged and older participants in the US. In the same study (Fernandez et al., 2016), higher objective health literacy, assessed using selected questions from the TOFHLA, was counterintuitively associated with a reduction in self-breast examination (OR = 0.37, 95% CI 0.19 to 0.73). All other preventative services examined were not associated with TOFHLA score (Fernandez et al., 2016). Using participants from ELSA, Kobayashi, Wardle, and von Wagner (2014), found that adequate health literacy (defined as scoring 4/4 on the health literacy test) was “borderline” significantly associated with completing a home colorectal cancer screening test (OR adjusting for age, educational attainment and wealth = 1.20, 95% CI 1.00 to 1.44) when compared to participants who scored ≤3. Another study, using a sample of participants from the US, found that scores on the REALM did not predict colorectal cancer screening (Peterson, Dwyer, Mulvaney, Dietrich, & Rothman, 2007). However, this was a small study (total n = 99) and very few participants had limited health literacy (n = 29), therefore this study may lack power to identify an association.

A systematic review of the association between health literacy and cancer screening (Oldach & Katz, 2014) concluded that there was limited evidence of an association between health literacy and colorectal cancer screening, prostate examinations, cervical screening and breast cancer screening; however the authors stated that, for breast cancer screening, it was “trending in a positive direction” (Oldach & Katz, 2014). Breast cancer screening was also investigated in the systematic review by Berkman et al. (2011). They reported that there was moderate evidence for an association between low health literacy and lower probability of mammography screening.

1.4.4.3. Hospitalisation and emergency care

There is evidence that low health literacy is associated with increased rates of emergency care and hospitalisation (Adams et al., 2009; Baker et al., 1998; Berkman et al., 2011). In one early study (Baker et al., 1998), a sample of 979 patients who attended health services in the US for non-urgent medical care were followed up for two years to test whether individuals with low health literacy, assessed using the TOFHLA, have a greater risk of hospital admission. Controlling for sex, race, health status, measures of socioeconomic status, and health insurance status, age was the strongest predictor of hospital admission (OR for patients ≥60 years, compared to those between 18 and 30 years = 2.91, 95% CI 1.52 to 5.53). The next strongest predictor was health literacy. The OR for individuals with inadequate, compared with adequate, health literacy was 1.69 (95% CI 1.13 to 2.53).

Another study (Adams et al., 2009) found evidence that those with low health literacy were less likely to use community health services, but were more likely to have been hospitalised in the last 12 months. In a sample of 2,824 Australian participants aged 15 years and older, compared to those who scored 4-6 on the Newest Vital Sign, those who scored 0-3 were less likely to visit a primary care provider (OR = 0.6, 95% CI = 0.4 to 0.7), and a hospital clinic (OR = 0.8, 95% CI 0.6 to 0.97). However, those who scored 0-3 on the Newest Vital Sign were more likely to report having been hospitalised in the past 12 months (OR = 2.2, 95% CI 1.1 to 4.5). It is possible that individuals with limited health literacy may not have the skills and knowledge required to know when to use community health services and therefore may rely more on emergency care.

1.5. Summary

This chapter provided an introduction to the concept of health literacy and how health literacy is measured. The research reviewed in this chapter showed that better health literacy has been found to be associated with various aspects of better health. In Chapter 2, I will introduce the concept of cognitive ability and show that, like health literacy, cognitive ability is strongly associated with various aspects of health.

2. Cognitive ability

Cognitive ability is a composite term for a broad range of mental capabilities involved in processing information, learning, and solving problems (Blazer, Yaffe, & Liverman, 2015; Gottfredson, 2004). These capabilities are thought to be critical for successfully functioning in everyday life (Blazer et al., 2015; Gottfredson, 2004). People vary in their level of mental capabilities. Whereas some individuals struggle learning new things and solving problems, others excel. An individual's level of cognitive ability has been found to have real world consequences. Individuals who have higher cognitive ability tend to do better in life (Gottfredson, 2004). For example, they tend to achieve higher educational qualifications, get higher paying jobs, obtain a higher socioeconomic status, and obtain better overall health (Gottfredson, 2004). The association between cognitive ability and health is the focus of this chapter. Before providing a review of the literature on cognitive ability and health, I will briefly define cognitive ability, detail how cognitive ability is assessed and provide a brief overview of the different theories of cognitive ability.

2.1. Defining cognitive ability

A number of different terms are used in the literature to describe this general mental capacity, including cognition, cognitive function(s), intelligence, general intelligence, or simply *'g'*. Linda Gottfredson defined intelligence as:

> …a very general mental capability that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience. It is not merely book learning, a narrow academic skill, or test-taking smarts. Rather, it reflects a broader and deeper capability for comprehending our surroundings— "catching on", "making sense" of things, or "figuring out" what to do. (Gottfredson, 1997, p. 13)

This definition was agreed upon and signed by 52 intelligence researchers (Gottfredson, 1997). Cognitive ability, according to Gottfredson and colleagues, is a general ability to “learn, reason and solve problems” (Gottfredson, 2004; Gottfredson & Deary, 2004). It is both content- and context-free (Gottfredson, 2004; Gottfredson & Deary, 2004). This general ability therefore plays a role in many different aspects of life, especially those that involve new and complex situations, such as those faced when managing one’s own health (Gottfredson, 2004; Gottfredson & Deary, 2004).

2.2. Measuring cognitive ability

Cognitive ability is not directly observable and therefore we use cognitive tests to measure cognitive ability. Cognitive tests are standardised assessments of specific mental capabilities (Salthouse, 2010b). These tests are designed to assess an individual’s maximum, rather than typical, mental functioning (Salthouse, 2012). There are thousands of different cognitive tests available designed to measure a broad range of different cognitive skills. An example of some of the types of cognitive tests that are commonly used are shown in Figures 2.1 and 2.2. Some tests are very short and take only a couple of minutes to administer, other tests can take up to an hour; some well-established tests come with validation information and normative data, others do not; some need to be administered face-to-face, one-to-one by an expert tester, others can be group-administered; some are paper-and-pencil tests, others are computer tests (Lara et al., 2015; Mathers et al., 2015).

Cognitive tests are often grouped by which cognitive domain they were designed to assess. A brief description of some of the most commonly assessed cognitive domains is provided below (Lara et al., 2015; Mathers et al., 2015):

- *Executive function:* Goal-directed behaviours, such as abilities to plan, organise and switch attention. Tests often involve individuals following a rule and ignoring irrelevant information. A commonly used test is categorical (animal) fluency, where participants are to name as many animals as possible in 60 seconds.
- *Declarative memory (also referred to as episodic memory):* The ability to learn and later remember information. Tests often require individuals to remember some information (e.g., a list of words, or a series of patterns) and recall this information immediately and again after a delay.
- *Reasoning:* The ability to think logically and solve abstract and novel problems. Tests usually require individuals to find the missing piece in a sequence by identifying the pattern and applying the rule (e.g., Figure 2.1).
- *Processing speed:* How quickly one can process information. Tests of processing speed require individuals to complete an easy task, such as copying symbols, as quickly as possible (e.g., Figure 2.2).
- *Visuospatial ability:* The ability to use and manipulate visual and spatial information. Tests usually require participants to physically or mentally manipulate objects in 3-dimensional space.
- *Working memory:* The ability to temporarily store and manipulate information. Tests often require individuals to remember a sequence (e.g., of numbers) and to perform some action on this sequence (e.g., saying them in the reverse order).

Some cognitive tests were designed to measure a specific cognitive domain. However, completing a cognitive test is likely to tap many different cognitive domains. Equally, no one cognitive test is a detailed assessment of a specific cognitive domain. To comprehensively assess cognitive ability, multiple tests of the same cognitive domain should ideally be administered (Lara et al., 2015; Mathers et al., 2015). Below I will describe some of the most commonly used assessments of cognitive ability.

2.2.1. Wechsler tests

One of the most commonly used assessments in cognitive research is the Wechsler Adult Intelligence Scale (WAIS). The fourth and newest edition of the WAIS (Wechsler, 2008) consists of 15 subtests assessing a diverse set of cognitive domains. Tests include the Block Design test which is designed to assess visuospatial ability and involves manipulating red and white blocks to match a pattern; tests of General Knowledge and Vocabulary designed to assess verbal comprehension; and the Symbol Search test which measures processing speed by requiring participants to identify, as quickly as possible, whether a target symbol appears in a row of symbols (Wechsler, 2008). The WAIS-IV includes a Matrix Reasoning Test and a Coding test, similar to the examples shown in Figures 2.1 and 2.2. There is also a separate Wechsler test battery, the Wechsler Memory Scale IV (Wechsler, 2009), which is designed to measure different kinds of memory, including working memory, verbal, visual and spatial long-term memory.

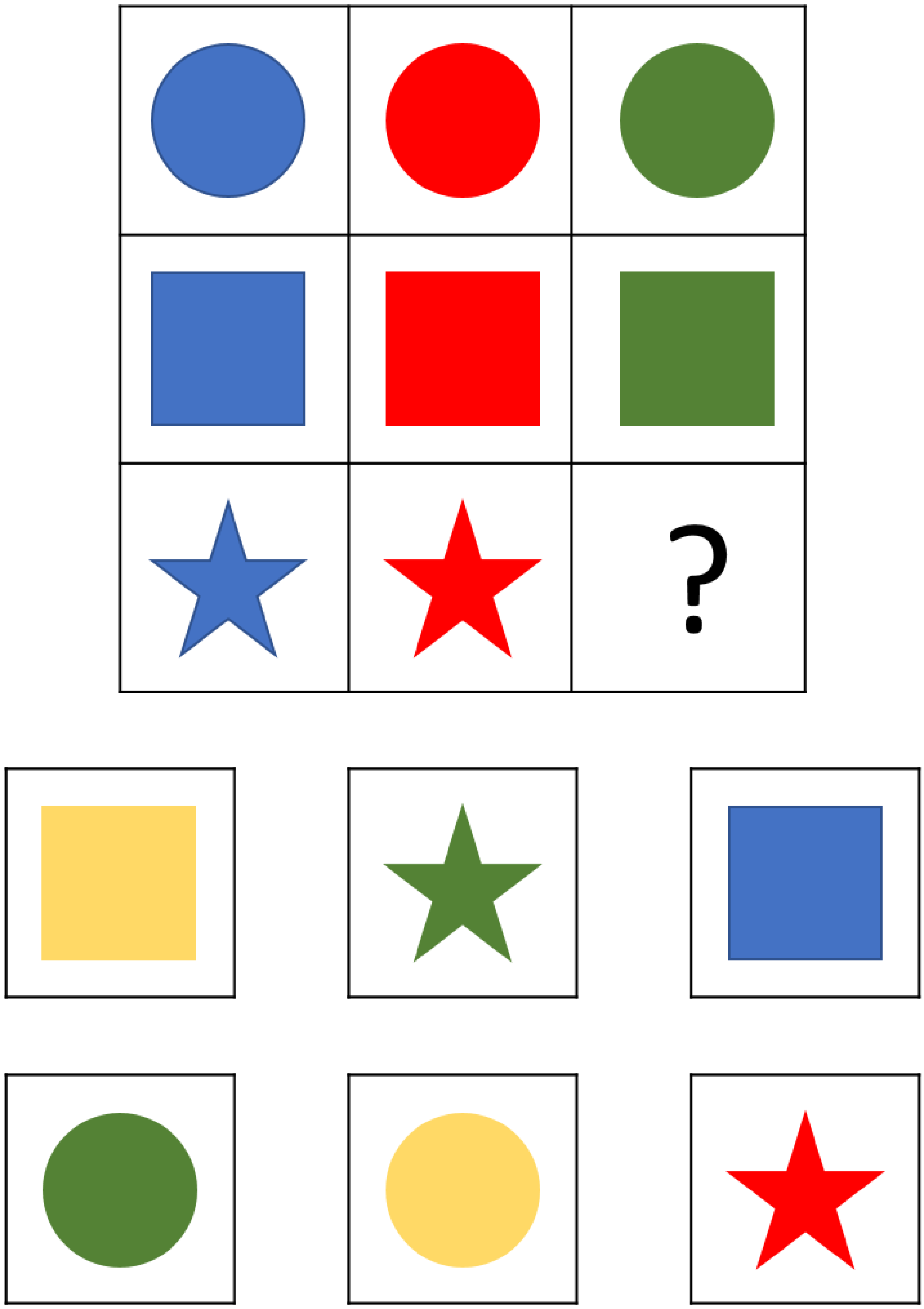

Figure 2.1. Example of the type of materials used in a matrix reasoning task, which is often used to assess reasoning. Participants are required to identify the pattern and then select which piece completes the pattern.

The Wechsler tests are well established, comprehensive cognitive tests, and the test developers provide technical manuals on the validation of the tests and normative data. The Wechsler tests, and other neuropsychological test batteries such as the Delis-Kaplan Executive Function System (Delis, Kramer, Kaplan, & Holdnack, 2004) are often considered the gold standard cognitive assessments. However, these test batteries are expensive to purchase, time-consuming to administer, and are not suitable for all research studies as administration requires one-to-one, face-to-face assessments to be carried out by a trained psychologist (Lara et al., 2015; Mathers et al., 2015).

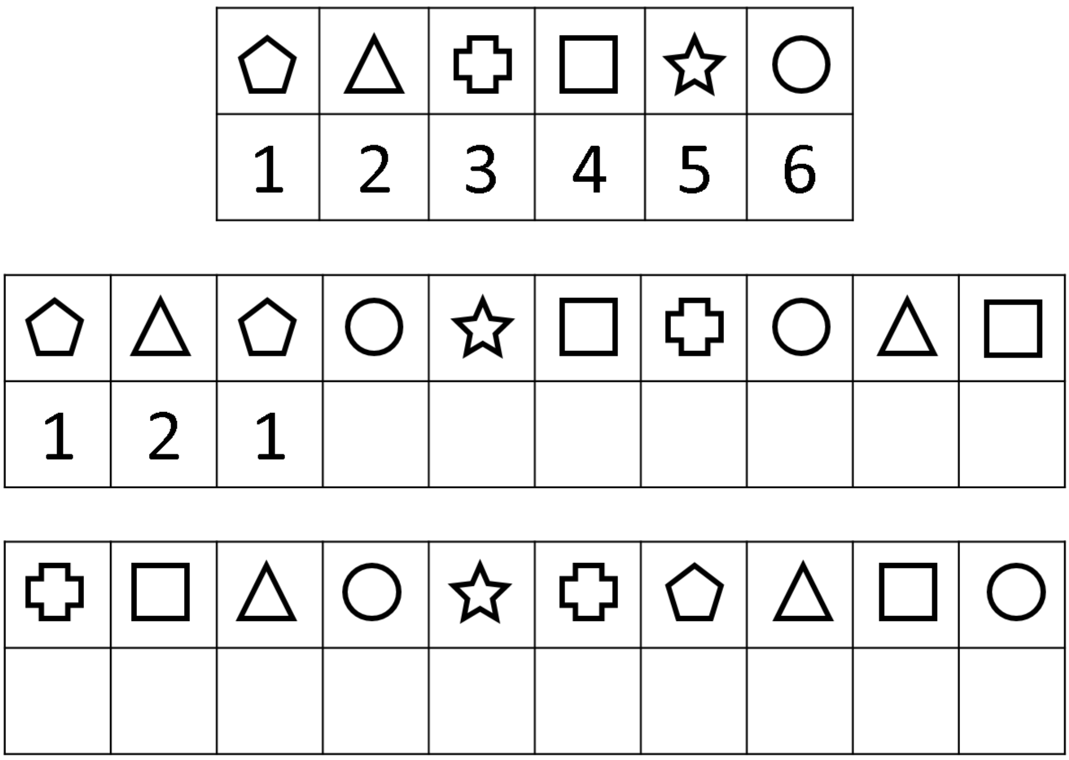

Figure 2.2. Example of a substitution test, which is commonly used as a test of processing speed. The participant is to write the number that is paired with the shape in the empty box as quickly as possible.

2.2.2. Cognitive screening tools

Another popular method of assessing cognitive ability in research is using cognitive screening tools, which are brief measures of global cognitive function designed to identify individuals who may have a cognitive impairment (Ismail, Rajji, & Shulman, 2010). These tests are much quicker to administer than neuropsychological assessments but provide a crude measure of cognitive functioning. Popular among these tests is the MMSE (Folstein et al., 1975) which is a 3-5 minute 30-item test that requires participants to, for example, remember three words over a brief delay, copy a shape, and follow a written command. In relatively healthy adults, the MMSE can be prone to ceiling effects (e.g., most people score full marks). Longer screening assessments, which are less prone to ceiling effects are also available, such as the Addenbrooke's Cognitive Examination III (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013).This test has slightly harder items, such as remembering a name and an address over a delay and drawing a clock (Hsieh et al., 2013).

2.2.3. Other tests of cognitive ability

The cognitive assessments used in many studies examining the association of cognitive ability and health, which are described below in Section 2.4, did not originally set out to investigate the association between cognitive ability and health. Instead, these studies assessed intelligence in childhood or early adulthood for other purposes, and these scores were subsequently used to investigate the association between intelligence in early life and health (as well as many other life outcomes). Typically, these studies assessed intelligence in childhood as part of their education (Deary, Gow, et al., 2007), or in early adulthood as part of army conscription (Batty et al., 2009). These standardised ability tests are often group administered and tend to measure abilities such as verbal and numerical reasoning and spatial ability. An example of the sorts of items used in these group-administered intelligence tests is shown in Figure 2.3. Performance on these ability tests correlate highly with performance on neuropsychological assessments, such as the WAIS tests (Deary, Gow, Pattie, & Starr, 2012).

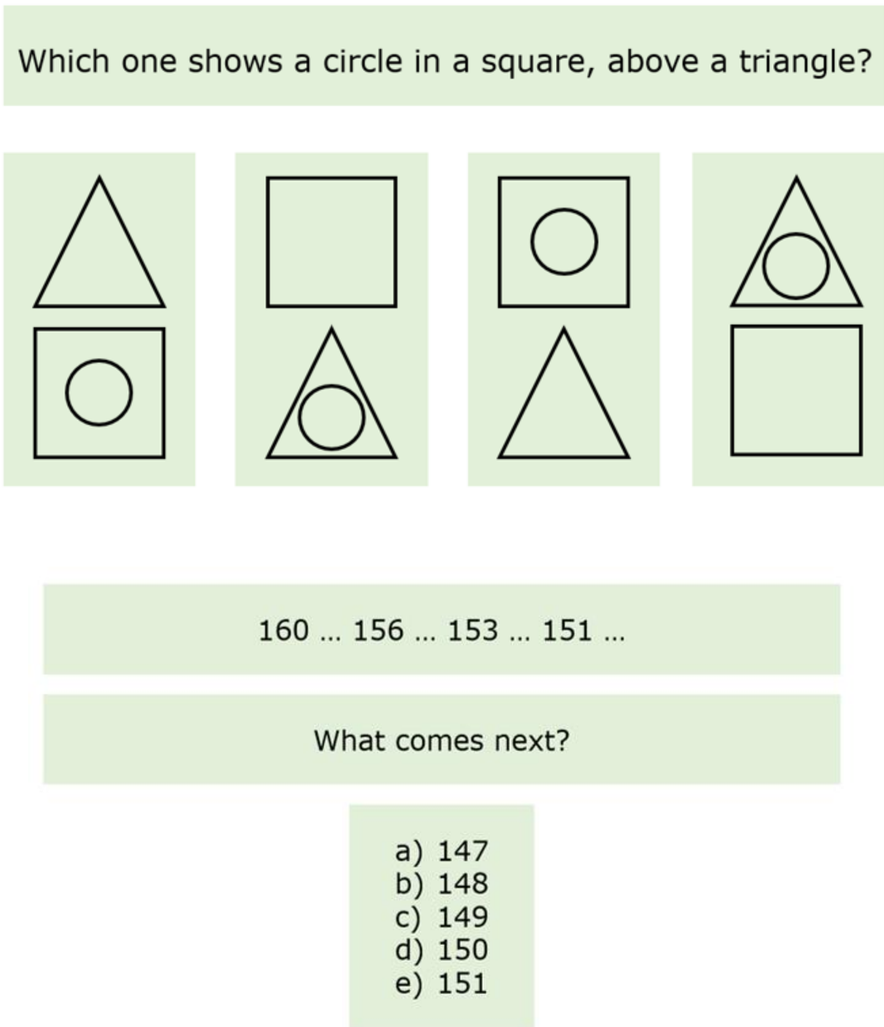

Figure 2.3. Example of the sorts of items that would be included in group-administered intelligence tests. These often assess verbal, visual and numerical reasoning skills.

2.3. Theories of cognitive ability

The most commonly cited theories of cognitive ability are Spearman's theory of general intelligence and Cattell and Horn's theory of fluid and crystallised ability. In the next two sections, I will briefly describe these theories.

2.3.1. General intelligence

Scores on almost all cognitive tests are positively correlated. That is, individuals who do well on one cognitive test tend to do well on them all. This phenomenon, which is one of the most replicated findings in psychological research, was first discovered by Charles Spearman in 1904 (Spearman, 1904). Spearman coined this positive correlation between cognitive tests as 'positive manifold' (Spearman, 1904).

To account for the covariance between cognitive tests, researchers often create a general measure of cognitive ability by combining scores on a diverse set of cognitive tests into one composite score (Salthouse, 2010b). Typically, scores on a range of cognitive tests are entered into a principal component analysis and scores on the first unrotated principal component are saved and used as a measure of general ability, often referred to simply as *'g'* (Deary & Batty, 2007). *g* factors created using entirely different cognitive test batteries correlated almost perfectly in one study ($r \geq 0.99$; Johnson, Bouchard Jr, Krueger, McGue, & Gottesman, 2004), and highly in another ($r \geq 0.77$; Johnson, te Nijenhuis, & Bouchard, 2008). These measures of general ability typically account for approximately 40% of the variance in a variety of cognitive test scores (Deary, Harris, & Hill, 2019).

Cognitive ability has been found to be a substantially stable trait with respect to individual differences across the life course. The correlation between scores on an intelligence test administered at age 11 and then again at age 79 was r = 0.63 (Deary, Whalley, Lemmon, Crawford, & Starr, 2000), and between age 11 and 90 was r = 0.54 (Deary, Pattie, & Starr, 2013).

Although covariance between a diverse set of cognitive tests has almost universally between found, some critics disagree with the use of a general measure of cognitive ability because they think reducing all mental ability to a single dimension is an oversimplification (Salthouse, 2010b). As outlined in Section 2.2, there are different domains of cognitive ability, such as processing speed, memory, and reasoning. Tests designed to measure one cognitive domain tend to correlate more highly with each other than they do with tests designed to assess other cognitive domains. This led some researchers to propose the theory of multiple intelligences (Gardner, 1983; Thurstone, 1938); however, this theory is not supported by the data because all cognitive domains tend to be highly correlated with each other (Deary, Penke, & Johnson, 2010).

The theory of general intelligence has been subsequently developed into a hierarchical model of general intelligence to account for the finding that correlations are higher between some cognitive tests and domains than others. This hierarchical model often portrays individual differences in intelligence at three levels (Carroll, 1993; Deary, Penke, et al., 2010; Salthouse, 2004). These three levels are shown in Figure 2.4. At the bottom are individual cognitive tests. These individual tests load highly on broader domains of cognitive ability (middle level; e.g., reasoning, processing speed), which in turn load highly on general intelligence (top level; Deary, Penke, et al., 2010; Deary et al., 2019; Salthouse, 2004). Most of the differences in cognitive ability between people is accounted for by general cognitive ability (*g* in Figure 2.4; Deary, Penke, et al., 2010; Deary, Weiss, & Batty, 2010; Salthouse, 2004). Apart for general cognitive ability, most of the individual differences between people are accounted for by differences in specific tests, and only a little is accounted for by broad domains of cognitive ability (Deary, Weiss, & Batty, 2010).

2.3.2. Fluid and crystallised ability

Whereas all tests of cognitive ability tend to correlate with each other, two distinct age trends have been found for different cognitive domains which led to the distinction between fluid and crystallised ability (Cattell, 1943; Horn, 1989, 1994). Fluid ability has been used to describe abilities that require effortful processing of novel, and often abstract, information (Deary & Batty, 2007; Salthouse, 2010a, 2010b, 2012). Cognitive domains, such as reasoning, some aspects of memory and speed of information processing are thought to assess fluid ability. Fluid abilities tend to peak in early adulthood and decline with increasing age (Salthouse, 2010a, 2010b, 2012). Timothy Salthouse and colleagues collected data on a range of cognitive tests covering a number of different cognitive domains in a large sample of adults aged 20 to 90 years (Salthouse, 2010a, 2010b, 2012). The cross-sectional age trends for vocabulary knowledge, reasoning, spatial visualisation, memory and speed are shown in Figure 2.5. For fluid abilities—that is reasoning, spatial visualisation, memory and speed—a negative linear association is seen with increasing age. The age association for processing speed is especially strong. Individuals in their 70s and 80s perform 1.5 to 2 standardised deviations lower on tests of processing speed than that of 20-year olds (Salthouse, 2010a, 2010b, 2012).

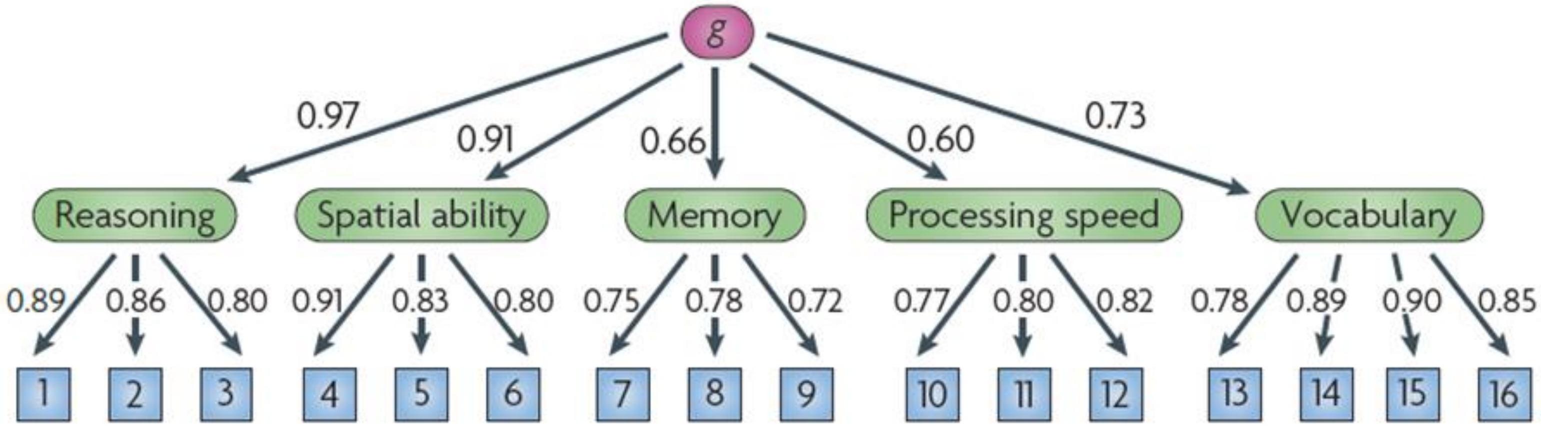

Figure 2.4. Hierarchical structure of intelligence. The bottom level (blue boxes) are individual cognitive tests. These cognitive tests load highly on domains of cognitive ability (level two; green boxes). In turn, cognitive domains load highly on general cognitive ability (‘*g*’ at top level; pink box). Adapted, with permission, from Deary, Penke and Johnson (2010).

In contrast, crystallised ability is information acquired as a result of previous processing carried out in the past (Deary & Batty, 2007; Salthouse, 2010a, 2010b, 2012). Assessments of crystallised ability tend to measure general knowledge and vocabulary skills. A distinctly different age pattern is seen for vocabulary, compared to all over cognitive domains shown in Figure 2.5. Crystallised ability is much more robust to the effects of ageing and tends to remain relatively stable, or even increases a little until around the age of 60, and then mean scores show a slight reduction at older ages (Salthouse, 2010a, 2010b, 2012). This distinction between fluid and crystallised age trends is robust and has been reported in other studies (Salthouse, 2010b; Schaie, 1996).

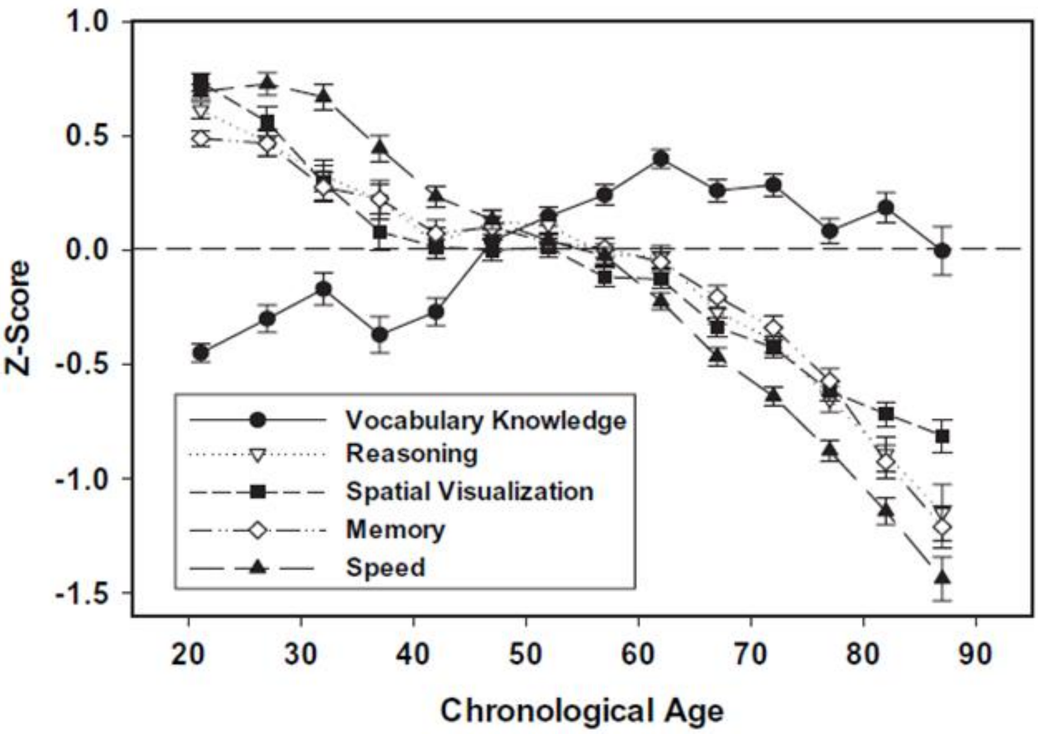

Figure 2.5. Cross-sectional age trends for five cognitive domains. Reprinted, with permission, from Salthouse (2010a).

Although fluid and crystallised ability show different age patterns, they correlate highly with each other and therefore this theory should not be considered as incompatible with the theory of general intelligence (Deary & Batty, 2007).

2.4. Cognitive ability and health

Evidence for an association between health literacy and health was provided in Section 1.4. In this section, I will show that there are associations between cognitive ability and health. Before reviewing the literature, it is important to note that this section will focus on studies that investigate cognitive ability as a correlate or predictor of health outcomes (e.g., lower cognitive ability predicting future diagnosis of hypertension). There is a wealth of research examining health indicators as predictors of cognitive level and cognitive decline (e.g., a diagnosis of hypertension predicting cognitive decline; for a review, see Blazer et al., 2015; Corley, Cox, & Deary, 2018). This thesis will focus on cognitive ability as a risk factor for poor health. However, it is possible that poor cognitive ability leads to poor health, and that poor health leads to greater cognitive decline (Blazer et al., 2015; Corley et al., 2018).

Cognitive ability has been found to be associated with many aspects of health (Gottfredson, 2004). Managing one's health, which Linda Gottfredson referred to as the "job of being a patient" (Gottfredson, 2004), requires the ability to learn new information about health, make decisions regarding health management, and reason and problem solve (Gottfredson, 2004). Therefore, successful health management will require general cognitive ability (Gottfredson, 2004; Gottfredson & Deary, 2004).

Cognitive epidemiology is the study of the association between prior cognitive ability and health (Deary, 2012). Lower cognitive test scores early in life are investigated as risk factors for poor health, disease and death (Deary & Batty, 2007). Individuals with higher cognitive ability early in life tend to be healthier later in life (Corley et al., 2018). Lower cognitive ability test scores have been found to predict a whole range of health indicators in later life, including being more likely to take part in unhealthy behaviours, poorer overall health, and increased rates of morbidity and mortality. Section 2.4 will review the literature investigating the association between cognitive ability and health.

2.4.1. Cognitive ability and mortality

One of the first and most consistent findings in cognitive epidemiology was that cognitive ability scores predict mortality. Lower cognitive ability in childhood or early adulthood is associated with a greater risk of all-cause mortality (Batty, Deary, & Gottfredson, 2007; Batty et al., 2009; Calvin et al., 2011; Christensen, Mortensen, Christensen, & Osier, 2016; Čukić, Brett, Calvin, Batty, & Deary, 2017; Twig et al., 2018). A systematic review and meta-analysis (Calvin et al., 2011) of intelligence in youth and risk of all-cause mortality conducted using data from 16 longitudinal studies in over 1 million participants found that a one SD advantage in cognitive test scores was associated with a 24% reduction in the risk of all-cause mortality (HR = 0.76, 95% CI 0.75 to 0.77; follow-up range 16 to 79 years). Čukić et al. (2017) investigated the association between performance on an intelligence test at age 11 and all-cause mortality over a 68-year follow-up using a near-entire (94%) population born in Scotland in 1936. This study found that there was a slightly stronger association between childhood IQ and deaths occurring before age 65 (HR per 1 SD increase in intelligence test score = 0.76, 95% CI 0.74 to 0.77) than for deaths occurring after 65 (HR = 0.79, 95% CI 0.78 to 0.80).

The association between cognitive ability and cause-specific mortality has also been investigated (Batty et al., 2009; Calvin et al., 2011; Christensen et al., 2016; Twig et al., 2018). Lower cognitive ability in early life has been found to predict increased risk of dying due to cardiovascular disease, respiratory disease, smoking related cancers, suicide and homicide (Batty et al., 2009; Calvin et al., 2017; Christensen et al., 2016; Twig et al., 2018). The early life intelligence-mortality association was especially strong for deaths due to respiratory disease (Calvin et al., 2017; Christensen et al., 2016) and was much weaker, and sometimes non-significant, for deaths due to cancer (Batty et al., 2009; Calvin et al., 2017; Christensen et al., 2016).

Using a sample of over 2 million individuals who completed an intelligence test administered as part of the Israeli army recruitment assessment, Twig et al. (2018) tested whether cognitive ability in adolescence (age 16-19 years) was associated with cardiovascular- and diabetes-related deaths over a median of 19.2 years follow-up. Compared to those who scored in the highest quintile on an intelligence test, those who scored in the lowest quintile had increased risk of cardiovascular disease-related mortality (HR = 1.76, 95% CI 1.52 to 2.04). The association between cognitive ability and risk of diabetes-related mortality was especially high. Risk of diabetes-related mortality was over 3 times greater (HR = 3.14, 95% CI 2.00 to 4.94) for those who scored in the lowest intelligence quintile, compared to those who scored in the highest intelligence quintile, even after adjusting for demographic and socioeconomic characteristics.

This evidence suggests that cognitive ability in early life may be more strongly associated with deaths that are possibly preventable, such as those that occurred before the age of 65 and those which are associated with health risk behaviours (e.g., respiratory disease, cardiovascular disease, diabetes, smoking related cancers).

2.4.2. Cognitive ability and morbidity

2.4.2.1. Cognitive ability and general health

Higher cognitive ability may be associated with reduced mortality risk because individuals with better cognitive ability may be healthier throughout life and suffer less from chronic disease than individuals with lower cognitive ability. Generally, individuals who score higher on cognitive ability tests in early life tend to have better physical and mental health, and suffer from fewer health conditions (Der, Batty, & Deary, 2009; Johnson, Corley, Starr, & Deary, 2011; Martin, Fitzmaurice, Kindlon, & Buka, 2004; Wraw, Deary, Gale, & Der, 2015; Wraw, Deary, Der, & Gale, 2016).

Using a sample of 7,476 participants from the National Longitudinal Study of Youth, 1979 cohort (NLSY79), Der et al. (2009) examined the association between cognitive ability test scores in adolescence and a range of health outcomes at age 40. Cognitive ability was assessed when participants were aged between 14 and 21 years with the Armed Forces Qualifications Test, which measured arithmetic, word knowledge, paragraph comprehension and mathematic skills. At the age of 40, these participants were asked about various aspects of their health. When adjusting for age and sex only, a one SD advantage in cognitive ability was associated with reporting better physical (beta = 0.17, SE = 0.012, $p < .001$) and mental (beta = 0.061, SE = 0.012, $p < .001$) health, assessed using the 12-Item Short-From Health Survey, and with fewer depressive symptoms (assessed using the Centre for Epidemiologic Studies Depression scale; beta = -0.186, SE = 0.011, $p < .001$). Higher cognitive ability in early life was also associated with lower odds of reporting a range of health conditions at age 40. A one SD higher cognitive ability score was associated with lower odds of reporting a diagnosis of chronic lung disease (OR = 0.78, 95% CI 0.67 to 0.90), heart problems (OR = 0.84, 95% CI 0.73 to 0.96), hypertension (OR = 0.84, 95% CI 0.79 to 0.89), diabetes (OR = 0.88, 95% CI 0.79 to 0.98), and arthritis/rheumatism (OR = 0.90, 95% CI 0.83 to 0.97), and with reduced odds of self-reporting 15 out of 33 health conditions, including chest pain, anaemia, frequent urinary tract infections, and back problems (ORs ranged from 0.88 to 0.67, $p \leq .031$). These associations were only slightly attenuated when additionally adjusting for childhood socioeconomic status (Der et al., 2009).

Higher cognitive ability, however, was not uniformly associated with better health at age 40 in this study. For some health outcomes, Der et al. (2009) found some evidence that higher cognitive ability in adolescence was associated with poorer health. A one SD increase in cognitive ability was associated with increased odds of self-reported chronic colds or sinus problems (OR = 1.11, 95% CI 1.05 to 1.17), high cholesterol (OR = 1.17, 95% CI 1.09 to 1.26), thyroid trouble or goiter (OR = 1.18, 95% CI 1.04 to 1.33), and tumours, growths, or cysts (OR = 1.37, 95% CI 1.10 to 1.70) at age 40 years.

Using the same sample of participants (the NLSY79), Wraw and colleagues (Wraw et al., 2015; Wraw et al., 2016) investigated whether there was a similar association between cognitive ability in youth and health a decade later, when these participants were aged approximately 50 years. Similar to the cognitive ability-health associations reported in Der et al. (2009) when these participants were aged 40, higher cognitive ability in youth was associated with better self-reported physical and mental health, and reduced odds of self-reporting a number of health conditions at age 50 (Wraw et al., 2015; Wraw et al., 2016). Wraw and colleagues (Wraw et al., 2015; Wraw et al., 2016) tested the attenuation of both childhood and adult socioeconomic status in the association between adolescent cognitive ability and adult health, whereas Der et al. (2009) only assessed the attenuating effects of childhood socioeconomic status. Childhood socioeconomic status only slightly attenuated the association between cognitive ability and health; however, additionally adjusting for adult socioeconomic status largely attenuated the association between cognitive ability in adolescence and health at age 50 years (Wraw et al., 2015; Wraw et al., 2016), suggesting that adulthood socioeconomic status may mediate the association between cognitive ability in youth and later health.

Even after adjusting for childhood age, sex, and childhood and adult socioeconomic status, cognitive ability remained significantly associated with some health outcomes (Wraw et al., 2015; Wraw et al., 2016). A one SD advantage in cognitive ability in youth was associated with reduced odds of self-reporting high blood pressure or hypertension (OR = 0.85, 95% CI 0.78 to 0.94), and having had a heart attack (OR = 0.69, 95% CI 0.51 to 0.93) at age 50 (Wraw et al., 2015); however, a one SD higher cognitive ability was also associated with increased odds of reporting pain or stiffness, or swelling of the joints (OR = 1.11, 95% CI 1.02 to 1.22; Wraw et al., 2015) and increased odds of reporting a diagnosis of depression (OR = 1.32. 95% CI 1.16 to 1.51; Wraw et al., 2016).

The studies reported above using the NLSY79 examined the association between cognitive ability and health in mid-life. A relationship between childhood cognitive ability and health at younger ages has also been found. The association between cognitive ability at age 7, assessed using the Wechsler Intelligence Scale for Children, and reporting any one of nine health conditions (heart disease, diabetes, cancer, asthma, arthritis, bleeding ulcer, tuberculosis, or hepatitis) at age 30 to 39 years was investigated using a sample of 663 participants from the United States

(Martin et al., 2004). A one SD increase in cognitive ability test scores was associated with a 33% reduction in reporting having any of the nine health conditions (OR controlling for sex, ethnicity, childhood socioeconomic status, low birth weight, learning disability at age 7, and educational attainment = 0.67, 95% CI 0.48 to 0.95), and with reporting a lower number of illnesses at age 30 to 39 years (beta = -0.07, SE = 0.03, *p* = .01; Martin et al., 2004).

The studies reviewed in this section suggest that individuals who have higher cognitive ability tend to fair better with respect to overall health. Higher cognitive ability is associated with better self-reported physical and mental health, and with lower odds of reporting a range of common health conditions. However, in the studies reviewed here, higher cognitive ability was not uniformly associated with better health. These studies also found that higher cognitive ability was associated with increased odds of reporting depression (Der et al., 2009; Wraw et al., 2016) and joint pain (Wraw et al., 2015).

Although these studies found that higher cognitive ability was associated with increased risk of subsequent depression (Der et al., 2009; Wraw et al., 2016), other research has found that higher cognitive ability is associated with reduced risk of depression (Gale, Hatch, Batty, & Deary, 2009; Gale, Batty, Tynelius, Deary, & Rasmussen, 2010; Hung et al., 2016; Koenen et al., 2009). The contrasting findings may be due to the way in which depression was assessed in these studies. In the NLSY79 study, depression was assessed by asking participants whether they had ever been diagnosed with depression (Der et al., 2009; Wraw et al., 2016), whereas studies that find a negative association between cognitive ability and depression (Gale et al., 2009; Gale et al., 2010; Hung et al., 2016; Koenen et al., 2009) have assessed depression using psychiatric diagnoses, hospitalisation for depression, or self-completion scales that assess symptoms of depression. Higher cognitive ability may be associated with being more likely to ever report a diagnosis of depression because individuals with higher cognitive ability may be more able to recognise their symptoms of depression and seek help (Wraw et al., 2016).

2.4.2.2. Cognitive ability and chronic disease

Some health conditions, such as hypertension and diabetes—which are common chronic conditions in middle-aged and older adults—are at least partly preventable (Hussain, Claussen, Ramachandran, & Williams, 2007). Preventing these conditions requires maintaining a healthy lifestyle such as maintaining a healthy weight, not smoking and taking part in regular physical activity (Hussain et al., 2007). Maintaining a healthy lifestyle and preventing chronic diseases requires individuals to follow recommended health guidelines, monitor their own health, and know when and how to take necessary action if, for example, they need to lose weight. Preventing chronic conditions like diabetes may be especially cognitively demanding tasks requiring use of problem solving and decision-making skills (Gottfredson, 2004; Gottfredson & Deary, 2004).

The association between cognitive ability and risk of developing chronic conditions has been investigated. Some studies have found an association between higher childhood cognitive ability and reduced rates of hypertension decades later (Batty, Deary, & Macintyre, 2007; Starr et al., 2004; Wraw et al., 2015). For example, when adjusting for sex, a one SD advantage in cognitive ability test scores assessed at age 10 was associated with a 10% reduction in likelihood of having hypertension at the age of 30 years (Batty, Deary, Schoon, & Gale, 2007a). Whereas this study (Batty, Deary, et al., 2007a) found that the association between cognitive ability and hypertension did not survive adjustment for sociodemographic variables, particularly educational attainment, others have found that the association between cognitive ability and hypertension was only slighted attenuated when adjusting for indicators of adult socioeconomic status (including education; Starr et al., 2004; Wraw et al., 2015). Others have found no relationship between cognitive ability in childhood and hypertension in midlife. Cognitive ability measured at age 11 was not associated with hypertension at approximately age 50 using a sample of over 7,000 individuals in the Aberdeen Children of the 1950s study (Batty, Deary, & Macintyre, 2007).

The relationship between cognitive ability and developing diabetes is also mixed. Some studies have found that early life cognitive ability predicts diagnosis of diabetes (Mõttus, Luciano, Starr, & Deary, 2013; Twig et al., 2014; Wraw et al., 2015); however, some of these associations did not survive adjustment for socioeconomic status or education (Mõttus et al., 2013; Wraw et al., 2015), suggesting that these measures of socioeconomic status may mediate the association between cognitive ability and diabetes. Using participants from the Lothian Birth Cohort 1936 (LBC1936) study, who had their cognitive ability measured when aged 11 and were followed up in older adulthood, one study (Mõttus et al., 2013) found that a one SD advantage in cognitive ability at age 11 was associated with reduced odds of both self-reported diabetes (OR = 0.74, 95% CI 0.60 to 0.91) and HbA1c-derived diabetes (OR = 0.76, 95% CI 0.64 to 0.92) at age 70, when adjusting for sex and age. These associations were attenuated and non-significant when also adjusting for other cardiovascular risk factors (BMI, high cholesterol, and hypertension; Mõttus et al., 2013). A large study of over 35,000 Israeli men, who completed an intelligence test at army enlistment when aged approximately 17 years and who were followed-up for a median of 5.5 years, found that risk for developing diabetes was over two times greater for participants who scored in the lowest (of four) cognitive ability category when compared to those who scored in the highest cognitive ability category, adjusting for a range of covariates including age, BMI, fasting glucose and a range of demographic and socioeconomic indicators (Twig et al., 2014).

Other studies have found that cognitive ability does not predict diabetes. Childhood intelligence did not predict diabetes status at age 30 years using participants from the 1970 British Cohort Study (Batty, Deary, et al., 2007a) or aged about 50 years using participants from the Aberdeen Children of the 1950s study (Batty, Deary, & Macintyre, 2007). Both these studies had relatively few individuals who developed diabetes during follow-up (82 cases, and 89 cases, respectively) and therefore these studies might have been underpowered to find an association.

The association between early life cognitive ability and developing the metabolic syndrome by middle-age was investigated using participants from the Vietnam Experience Study (Batty et al., 2008). The metabolic syndrome is a clustering of cardiovascular risk factors, including type 2 diabetes and hypertension. The Vietnam Experience Study is a cohort of previous US army recruits that had their intelligence assessed at entry to the army in early adulthood using an army aptitude test. Participants were classified as having metabolic syndrome if they had any three of the following: obesity, diabetes, high triglycerides, high cholesterol, high blood pressure and/or use of antihypertensive medication. In a model adjusting for age, army-rank, and a range of socioeconomic variables, a one SD increase in intelligence test score was associated with a 13% reduction in the risk of developing metabolic syndrome in mid-life (OR = 0.87, 95% CI 0.78 to 0.98; n = 4,157).

Next, the authors investigated whether metabolic syndrome played a mediating role between intelligence and mortality (Batty et al., 2008). The authors created a PCA-derived index of metabolic syndrome by entering all the components of metabolic syndrome into a PCA and saving the first unrotated principal component. The age-adjusted association between intelligence and cardiovascular disease mortality (HR

= 0.75, 95% CI 0.59 to 0.96) was reduced by 12% when adjusting for the conventionally derived metabolic syndrome (HR = 0.78, 95% CI 0.61 to 1.00), and by 32% when adjusting for the PCA-derived metabolic syndrome (HR = 0.83, 95% CI 0.65 to 1.06). This finding suggests that the abilities assessed with tests of intelligence are important skills for managing one's own health and preventing disease, which in turn, is associated with lower risk of mortality (Batty et al., 2008).

Given the associations between cognitive ability and cardiovascular risk factors, it is unsurprising that links between cognitive ability and cardiovascular disease have been reported. One study using a sample of 6,910 Danish men who had their cognitive ability measured when aged 12 years found that poorer cognitive ability in early life predicted coronary heart disease, but not stroke, when followed-up in middle-age (Batty, Mortensen, Nybo Andersen, & Osler, 2005). There were only a small number of stroke events (n = 93) in this study, which may be one reason why no association was found between intelligence and stroke (Batty et al., 2005). A systematic review and meta-analysis of the association between cognitive ability and risk of stroke found that a 1 SD decrement in cognitive ability score was associated with a 15% (RR = 1.15, 95% CI 1.10 to 1.21) higher risk of stroke, based on 12 studies with 89,899 participants and 3,043 stroke events (Rostamian, Mahinrad, Stijnen, Sabayan, & de Craen, 2014). Most of the studies used in this review (Rostamian et al., 2014) assessed cognitive ability in older age, rather than cognitive ability in early life, and therefore the measure of cognitive ability in this meta-analysis may reflect cognitive decline as a result of subclinical vascular disease, rather than premorbid (prior) cognitive ability.

Hart et al. (2004) investigated the association between intelligence test scores in childhood and cardiovascular disease events (hospital admissions and deaths) through to old age in 928 individuals. For a 1 SD decrease in cognitive ability, the sex-, social class-, and deprivation-adjusted relative risk of cardiovascular disease was not significant (RR = 1.08, 95% CI 0.97 to 1.21). This study (Hart et al., 2004) examined the association between cognitive ability and relative risk of cardiovascular disease before and after the age of 65. For events occurring before the age of 65, there was a 19% (adjusted RR = 1.19, 95% CI 1.03 to 1.38) increased relative risk of cardiovascular disease per 1 SD decrease in cognitive ability; however, there was no association when using events occurring after the age of 65 (adjusted RR = 0.98, 95% CI 0.83 to 1.15).

The disease management hypothesis has been proposed as a possible explanation for the association between cognitive ability and chronic disease (Batty et al., 2005; Batty, Deary, & Gottfredson, 2007). This hypothesis posits that chronic disease management can be considered a cognitive task (Batty et al., 2005; Gottfredson, 2004). Individuals with higher cognitive ability are more able to manage their health and reduce the risk of chronic disease because they have the general learning and reasoning skills needed to successfully monitor and respond to their health needs (Batty et al., 2005; Batty, Deary, & Gottfredson, 2007; Gottfredson, 2004; Gottfredson & Deary, 2004).

2.4.3. Cognitive ability and health behaviours

One possible explanation for the association between and cognitive ability and death and disease is that people with higher cognitive ability may exhibit healthier behaviours throughout life which reduces the risk of morbidity and mortality (Deary, Penke, et al., 2010; Deary, Weiss, et al., 2010). A wealth of research has examined the association between cognitive ability and taking part in health promoting behaviours. Individuals with higher mental ability in early life tend to be more likely to take part in regular physical activity—especially vigorous exercise—in middle age (Batty, Deary, Schoon, & Gale, 2007b; Wraw, Der, Gale, & Deary, 2018). Using participants from the NLSY79, a higher cognitive ability in adolescence was associated with greater odds of being able to participate in strength training, moderate cardiovascular activity, and vigorous cardiovascular activity at age 50 years, even after adjustment for age, sex, ethnicity, and childhood and adult socioeconomic status (Wraw et al., 2018).

In addition to investigating the association between cognitive ability and odds of being able to participate in physical activity, this study (Wraw et al., 2018) also examined the association between early life cognitive ability and amount of time spent taking part in physical activity per week at age 50. For each type of exercise (i.e., strength training, moderate cardiovascular activity, and vigorous cardiovascular activity), higher cognitive ability in early life was associated with being less likely to be inactive, and also with being less likely to do a lot of exercise in mid-life (Wraw et al., 2018). For example, compared with those who completed 1 to 3 strength training sessions per week—which is the recommended weekly amount of strength training—a one SD advantage in cognitive ability in adolescence was associated with lower odds of reporting not taking part in any strength training sessions per week (OR = 0.91, 95% CI 0.82 to 0.99, adjusting for age, sex, ethnicity, and childhood and adult socioeconomic status), and lower odds of reporting doing 4 or more strength training sessions per week (OR = 0.77, 95% CI 0.68 to 0.88). The results of this study may indicate that individuals with higher cognitive ability are more likely to follow the recommended guidelines regarding physical activity (Wraw et al., 2018).

A relationship between higher cognitive ability in youth and better eating habits in midlife has also been reported. Individuals with higher on cognitive ability in early life are less likely to be overweight or obese in midlife (Batty, Deary, & Macintyre, 2007; Batty, Deary, et al., 2007a), suggesting that they are more likely to be eating a healthy and balanced diet. People with higher intelligence in childhood tend to report eating more of the foods thought to be good for you. Using 8,282 participants from the 1970 British Cohort Study (Batty, Deary, et al., 2007b), a one SD advantage in verbal ability measured at age 10 was associated with being more likely to report frequently eating fresh fruit, cooked vegetables, salads/raw vegetables, wholemeal bread, poultry, and fish, and less likely to report frequently eat cakes or biscuits, and chips at age 30 in unadjusted models. When adjusting for sex, childhood and adult socioeconomic status, educational qualifications, and annual net earnings these associations tended to be attenuated and the effect sizes were small; however, in this fully-adjusted model a one SD advantage in verbal ability remained associated with being more likely to report frequently consuming fresh fruit (OR = 1.09, 95% CI 1.03 to 1.14), cooked vegetables (OR = 1.18, 95% CI 1.12 to 1.25), salad or raw vegetables (OR = 1.09, 95% CI 1.03 to 1.14), wholemeal bread (OR = 1.05, 95% CI 1.00 to 1.10), and fish (OR = 1.16, 95% CI 1.10 to 1.27), and being less likely to frequently consume chips (OR = 0.91, 95% CI 0.87 to 0.97; Batty, Deary, et al., 2007b).

Higher cognitive ability, however, is not uniformly associated with healthy eating habits. There is also some evidence that a higher cognitive ability is associated with some eating habits that are thought to be unhealthy. Using participants from the NLSY79 sample (Wraw et al., 2018), a 1 SD higher intelligence in youth was associated with being more likely to skip meals (OR = 1.16, 95% CI 1.07 to 1.26) and more likely to snack between meals (OR = 1.38, 95% CI 1.24 to 1.55) at age 50 when adjusting for measures of socioeconomic status (Wraw et al., 2018).

The relationship between cognitive ability and smoking status and alcohol consumption has also been investigated. Individuals with higher cognitive ability in early life have been found to be less likely to report having ever smoked (Batty, Deary, & Macintyre, 2007; Batty, Deary, et al., 2007a; Hemmingsson, Kriebel, Melin, Allebeck, & Lundberg, 2008; Wraw et al., 2018). However, one study using a cohort of older adults born in 1936 found no association between cognitive ability test scores at age 11 and whether participants reported ever smoking (M. D. Taylor et al., 2003). Given the age of these participants, it is possible that no association was found between cognitive ability and ever smoking because the negative effects of smoking were less well known when this sample were young. This study (M. D. Taylor et al., 2003) and others (Batty, Deary, et al., 2007a) have found that, in ever smokers, individuals with higher early life cognitive ability were more likely to quit smoking. In ever smokers, those with higher cognitive ability may have made the decision to quit after realising the harms of smoking. Adulthood socioeconomic status tended to at least partially attenuate these associations between cognitive ability and smoking (Batty, Deary, & Macintyre, 2007; Batty, Deary, et al., 2007a; Wraw et al., 2018).

The relationship between cognitive ability and alcohol consumption is complex. Individuals with higher cognitive ability have been found to be more likely to drink alcohol in mid-to-later life (Johnson et al., 2011; Wraw et al., 2018). A one SD higher cognitive ability in adolescence was associated with a 23% increased odds of reporting having had an alcoholic drink in the last 30 days at age 50 using participants from the NLSY79 (adjusting for age, sex, ethnicity, childhood and adult socioeconomic status; Wraw et al., 2018). A higher childhood IQ was associated with drinking more units of alcohol per week in old age (standardised beta = 0.09, $p < .01$; adjusting for sex, childhood deprivation, father’s education, father’s social class, own education, and own social class) using LBC1936 participants (Johnson et al., 2011). When examining the number of alcoholic drinks consumed per week, Wraw et al. (2018) found a U-shaped association between cognitive ability in adolescence and number of alcoholic drinks consumed per week at age 50. Whereas higher cognitive ability was associated with consuming fewer alcohol drinks per week in the lower half of cognitive ability scores, higher cognitive ability was associated with consuming more alcoholic drinks per week in the upper half of cognitive ability scores (Wraw et al., 2018).

Although higher cognitive ability has been found to be associated with being more likely to drink alcohol and to drink more alcohol, lower cognitive ability has been associated with more risky drinking behaviours. Those with higher cognitive ability in early life were less likely to report getting hangovers, an indicator of binge drinking (Batty, Deary, & Macintyre, 2006), and more likely to report heavy drinking (Batty, Deary, & Macintyre, 2007; Wraw et al., 2018) in middle age. A one SD higher cognitive ability in adolescence was associated with a 33% reduction in the odds of reporting having had 6 or more drinks on one occasion in the past 30 days when aged 50 using participants from the NLSY79, adjusting for age, sex and ethnicity (Wraw et al., 2018). Using data from 7,183 participants from the Aberdeen Children of the 1950s, a one SD higher cognitive ability was associated with reduced odds (sex-adjusted OR = 0.89, 95% CI 0.84 to 0.94) of reporting "heavy drinking" in midlife, defined as consuming 4 or more alcoholic beverages 2-3 times per month or more in the past year (Batty, Deary, & Macintyre, 2007). Whereas these associations between cognitive ability and risky drinking behaviours tended not to be confounded by childhood socioeconomic status, these associations were attenuated and sometimes non-significant following adjustment for adult socioeconomic status suggesting that socioeconomic status may mediate the association between childhood cognitive ability and alcohol consumption in adulthood (Batty et al., 2006; Batty, Deary, & Macintyre, 2007; Wraw et al., 2018).

Individuals with high and low cognitive ability may have different drinking habits (Wraw et al., 2018). Whereas, individuals with higher cognitive ability may be more likely to drink, they may take part in moderate alcohol drinking, consuming only a small number of alcoholic drinks per occasion. On the other hand, individuals with lower cognitive ability may be more likely to take part in risky drinking behaviours such as binge drinking and problematic drinking (Wraw et al., 2018).

Although the results are mixed, the literature reported in this section suggests that individuals with higher cognitive ability in early life tend to be more likely to take part in health promoting behaviours such as regular physical activity, eating a healthy diet, and not smoking. The abilities assessed using tests of cognitive ability may be assessing the same underlying abilities that are required to self-manage health and take part in health promoting behaviours.

2.4.4. Cognitive ability and managing chronic disease

Taking part in health promoting behaviours are not only important for general health and for preventing chronic disease, they are also a crucial component of managing chronic diseases once a chronic condition has been diagnosed. The burden of chronic disease management is often placed on the patient, who is expected to do the majority of the day-to-day management of the condition. After diagnosis, chronic disease patients may be expected to make lifestyle changes, such as losing weight or stopping smoking or drinking alcohol; they may need to learn to follow complicated medication regimens, involving taking a large number of different medications at different times throughout the day; and they may need to monitor their symptoms and know when and how to take necessary actions when symptoms are aggravated. Managing chronic diseases may be especially cognitively demanding tasks, requiring, for example, constant self-monitoring and use of problem solving and decision-making skills (Gottfredson, 2004; Gottfredson & Deary, 2004).

Accordingly, researchers have investigated the association of cognitive ability with disease self-management, including adherence to medication (that is, taking medication as prescribed, including the correct number of doses and at the correct time), and following other medical advice such as abstaining from smoking and alcohol, and following dietary restrictions. Higher scores on tests of cognitive ability have been found to be associated with being more likely to adhere to medical treatment in patients with heart failure (Alosco et al., 2012; Hajduk et al., 2013), schizophrenia (Heinrichs, Goldberg, Miles, & McDermid Vaz, 2008), HIV (Hinkin et al., 2002; Hinkin et al., 2004), chronic obstructive pulmonary disease (O'Conor et al., 2019), type 2 diabetes (Rosen et al., 2003; Stilley, Bender, Dunbar-Jacob, Sereika, & Ryan, 2010), hypertension (Salas et al., 2001), hyperlipidaemia (Stilley, Sereika, Muldoon, Ryan, & Dunbar-Jacob, 2004), and breast cancer (Stilley et al., 2010). Higher cognitive ability test scores have also been found to be associated with medication adherence in a community dwelling sample of older adults taking a range of different medications, including for hypertension, hyperlipidaemia and arthritis (Insel, Morrow, Brewer, & Figueredo, 2006).

One study (Hinkin et al., 2004) examined the relationship between cognitive impairment and adherence to highly active antiretroviral therapy (HAART) in 148 HIV-infected adults aged between 25 and 69 years (mean = 44.2). In this study, participants completed 8 cognitive tests assessing learning and memory, executive function, and processing speed. All cognitive tests scores were first converted to demographically corrected t-scores (mean = 50, SD = 10). Next, for each cognitive test, participants were assigned a “deficit score” ranging between 0 and 5 (t-score greater than or equal to 40 = 0; 35-39 = 1; 30-34 = 2; 25-29 = 2; 20-24 = 4; less than 20 = 5), with higher scores reflecting more cognitive impairment. Finally, participants were classed as having a global cognitive impairment if the mean deficit score across all 8 cognitive tests was greater than or equal to 0.5 (Hinkin et al., 2004). Participant’s adherence to HAART was monitored over a 4 week period using a medication event monitoring system, which is an electronic cap placed over a bottle of medication that records the date and time the medication bottle was opened. Participants who took at least 95% of their prescribed doses were classed as adhering to HAART (Hinkin et al., 2004). When adjusting for age, participants with cognitive impairment were 2.5 times more likely to be poor adherers to HAART (OR = 2.5, 95% CI 1.19 to 5.35) when compared to those with normal cognitive functioning (Hinkin et al., 2004).

Another study (O'Conor et al., 2019) examined the relationship between cognitive ability and adherence to chronic obstructive pulmonary disease (COPD) medication in 337 patients with COPD aged 55 years and older. In this study, a latent measure of fluid ability was created by saving scores from the first unrotated principal component from four tests thought to assess processing speed, working memory, episodic memory and executive function. This study also used the MMSE as an indicator of “global cognitive ability”, and animal naming as a measure of crystallised ability (I note that animal naming is also often used as a test of executive function, discussed in Section 2.2). Participants were classed as adherent to COPD medication if they scored ≥ 4.5 (equivalent to never or rarely forgetting to take a medication) on the Medication Adherence Reporting Scale (MARS), which is a self-reported instrument of adherence to inhaled medications (O'Conor et al., 2019).

Using the MARS, only 38.9% of participants in this study were adherent to COPD medication. Controlling for age, race/ethnicity, income, number of chronic conditions, and COPD severity, a one SD higher cognitive ability was associated with increased odds of being adherent to COPD medications (OR = 1.74, 95% CI 1.37 to 2.21).

In addition to medication adherence, this study (O'Conor et al., 2019) also examined the association between cognitive ability and other COPD self-management behaviours, including being able to correctly use different types of inhalers, regularly visiting COPD healthcare providers, and having had the flu vaccination in the last 12 months. Higher fluid cognitive ability was significantly associated with being able to correctly use a metered-dose inhaler and a dry-powder inhaler, and with being more likely to have visited a COPD healthcare provider within the last 12 months, after controlling for age, race/ethnicity, income, number of chronic conditions, and COPD severity. Higher MMSE score was associated with correct inhaler technique, whereas animal naming was not associated with any of the self-management behaviours examined (O'Conor et al., 2019).

Most of the studies examining the association between cognitive ability and treatment adherence are either cross-sectional or are prospective in which participants are followed-up for a relatively short amount of time (typically 1 to 6 months) to measure their adherence to treatment. Most of these studies assess cognitive ability after participants have been diagnosed with a chronic condition. Although these study designs enable us to determine whether an association between cognitive ability and treatment adherence exists, such studies do not inform on the possible causal pathways between cognitive ability and medication adherence. It is not clear whether lower cognitive ability leads to poorer adherence, or whether poorer adherence leads to lower cognitive ability, or whether some other variable influences both cognitive ability and treatment adherence.

One study (Wallert, Lissåker, Madison, Held, & Olsson, 2017), which is better suited to disentangle this pathway, assessed whether cognitive ability in adolescence predicted statin adherence approximately 30 years later in a sample of Swedish male participants who subsequently suffered a myocardial infarction (MI). Cognitive ability, which was assessed at army conscription when participants were aged 18-20 years, was measured using scores from the first unrotated principal component from a PCA of four tests assessing verbal ability, logical reasoning, non-verbal ability and technical understanding. This study identified all first MI patients who were prescribed statins for the first time when they were discharged from hospital (n = 2,613). Adherence to statins was estimated by calculating the number of pills obtained (obtained from prescription records), divided by the number of days during the observation period. This estimate is based on the assumption that the participants were required to take one pill per day. This ratio was multiplied by 100 to obtain the estimated percentage of days that participants were adherent to statins (Wallert et al., 2017). Participants were classed as adherent to statins if this ratio was 80% or higher. Controlling for age, age-squared, weight, comorbidities and employment status, a one SD advantage in adolescence cognitive ability was associated with a 15% increased odds of being adherent to statins (OR = 1.15, 95% CI 1.01 to 1.31). This association was slightly attenuated and no longer significant when additionally adjusting for other discharge medications and health-related behaviours (OR = 1.11, 95% CI 0.97 to 1.28; Wallert et al., 2017).

The research reviewed in Section 2.4.4 suggests that, in chronic disease patients, individuals with a higher cognitive ability are more likely to adherence to medical treatment, which is an important component of managing chronic disease symptoms. Adhering to complicated medical regimens may be a cognitively demanding task, and instead of being unwilling to adhere to treatment, chronic disease patients with lower cognitive ability may lack the cognitive skills required to follow such complicated treatment regimens (Gottfredson, 2004; Gottfredson & Deary, 2004).

2.4.5. Genetic associations between cognitive ability and health

Despite some mixed findings, the literature reviewed so far in Section 2.4 has shown that higher cognitive ability tends to be associated with a range of better health outcomes, including being more likely to take part in healthy behaviours, better general health, lower risk of developing chronic diseases, lower risk of mortality, and, in those who develop a chronic disease, greater treatment adherence. One possible reason for finding phenotypic associations between higher cognitive ability and better health is that cognitive ability and health may share genetic influences. That is, the same genetic variants that influence cognitive ability, may also influence various aspects of health.

Cognitive ability is substantially heritable (Deary et al., 2019; Haworth et al., 2010; Plomin & Deary, 2015). Twin studies have been used to measure the degree of heritability of cognitive ability (and other traits) by comparing the resemblance between pairs of monozygotic (identical) and dizygotic (non-identical) twins on a given trait (Boomsma, Busjahn, & Peltonen, 2002) Monozygotic twins share 100% of their DNA, whereas dizygotic twins share, on average, 50% of their DNA. Therefore, if the correlation between pairs of monozygotic twins is higher for a given trait than that of dizygotic twins, it is assumed that this is because the trait is heritable (Boomsma et al., 2002). The heritability of a trait can be estimated by calculating the difference between the size of the correlation between pairs of monozygotic twins and dizygotic twins, and then multiplying this difference by two (Boomsma et al., 2002). Twin studies have shown that approximately 50% of the variance in cognitive ability is due to differences in genes (Deary et al., 2019; Luciano, Weiss, Gale, & Deary, 2018). A meta-analysis of 152,197 monozygotic twin pairs and 158,626 dizygotic twin pairs found that the correlation for cognitive function in monozygotic twin pairs was 0.71, whereas the correlation in dizygotic twin pairs was 0.44; therefore this study estimated the heritability of cognitive ability to be 54% (Polderman et al., 2015).

Molecular genetic techniques have been used to understand the genetic architecture of cognitive ability. Genome-wide association studies (GWAS) test whether individual genetic variants are associated with a phenotype (i.e., a trait). Hundreds of thousands of genetic variants are each tested—usually using linear regression for continuous traits, or logistic regression for binary traits—for their association with the phenotype of interest (Deary et al., 2019). Because a large number of statistical tests are conducted, a stringent significance threshold is used; most commonly $p < 5x10^{-8}$ (Deary et al., 2019).

An early GWAS (n = 3,511) of cognitive ability identified no common genetic variants associated with cognitive ability (Davies et al., 2011); however, with increasing sample sizes, the specific genetic variants associated with cognitive ability are beginning to be identified (Davies et al., 2018; Savage et al., 2018). A meta-analysis of GWAS results of cognitive ability in 300,486 individuals identified 11,600 genetic variants, distributed across 148 independent regions of the genome, that were associated with cognitive ability test scores (Davies et al., 2018).

Following the wealth of evidence reporting a phenotypic association between cognitive ability and aspects of health, researchers have begun to investigate whether this phenotypic association may in part be due to there being genetic associations between cognitive ability and health. Generally, studies examining the shared genetic architecture between cognitive ability and health have found that some of the genetic variants that influence cognitive ability overlap with those that influence physical and mental health traits (Deary et al., 2019; Hill, Harris, & Deary, 2019).

Two genetic techniques—linkage disequilibrium (LD) score regression and polygenic profile scoring—can be used to estimate the genetic overlap between two phenotypes. Both these techniques utilise summary results from previous GWAS. In LD score regression (Bulik-Sullivan et al., 2015), the genetic correlations between two phenotypes are calculated by comparing whether the genetic variants found to be associated with one trait (e.g., cognitive ability) correlate with the genetic variants found to be associated with another trait (e.g., hypertension). Polygenic profile scoring involves using summary results from a GWAS of a specific trait (e.g., hypertension) and testing whether the common genetic variants found to be associated with this trait are also associated with the same (e.g., hypertension) or a different (e.g., cognitive ability) phenotype in an independent sample of participants (Purcell et al., 2009).

One study (Hagenaars et al., 2016) used these two techniques to explore the genetic associations of cognitive function and 24 health-related traits, including vascular diseases, neuropsychiatric disorders, and physical measures of health in 112,151 middle-aged and older UK Biobank participants. This study assessed cognitive ability with three brief tests of verbal-numerical reasoning (n = 36,035), reaction time (n = 111,484) and short-term memory (n = 112,067). Using LD score regression, negative genetic correlations were found between performance on a 13-item multiple-choice verbal-numerical reasoning test and ischaemic stroke (r_g = -0.23, SE = 0.09, p = .012), Alzheimer's disease (r_g = -0.39, SE = 0.12, p = .002), schizophrenia (r_g = -0.30, SE = 0.05, $p = 3.5 \times 10^{-11}$), and BMI (r_g = -0.12, SE = 0.03, $p = 2.0 \times 10^{-4}$). A positive genetic correlation was found between verbal-numerical reasoning and autism (r_g = 0.19, SE = 0.07, p = .005).

Lower verbal-numerical reasoning test scores were associated with higher polygenic risk for coronary artery disease (standardised beta (β) = -0.019, FDR-adjusted p = .0002), ischaemic stroke (β = -0.014, p = .0068), large vessel disease stroke (β = -0.013, p = .0155), Alzheimer's disease (β = -0.023, $p = 1.27 \times 10^{-5}$), major depressive disorder (β = -0.020, p = .0002) and schizophrenia (β = -0.062, $p = 7.73 \times 10^{-32}$). Lower verbal-numerical reasoning scores were associated with a higher polygenic profile for BMI (β = -0.027, $p = 3.34 \times 10^{-7}$), whereas higher verbal-numerical reasoning was positively associated with increased risk of autism (β = 0.023, $p = 1.43 \times 10^{-5}$) and a higher polygenic score for systolic blood pressure (β = 0.013, p = .0116). A similar pattern of results was found when using scores on the reaction time test and the short-term memory test; however, these associated tended to be weaker (Hagenaars et al., 2016). The results reported in Hagenaars et al. (2016) have subsequently been replicated in larger samples (Davies et al., 2018).

The results of this (Hagenaars et al., 2016) and other (Davies et al., 2018) studies demonstrate that there are substantial shared genetic influences between cognitive ability and a range of physical and mental health traits. The phenotypic associations reported between cognitive ability and health-related traits may therefore be partly due to shared genetic influences between cognitive ability and health (Deary et al., 2019; Hill et al., 2019).

2.5. Summary

To summarise, this chapter introduced the concept of cognitive ability and showed that cognitive ability is associated with many aspects of health. Although there are some mixed findings, individuals with higher cognitive ability tend to have better health. Higher cognitive ability has been found to be associated with lower risk of mortality (Section 2.4.1), better general health and lower risk of chronic diseases (Section 2.4.2), and being more likely to take part in health promoting behaviours, such as eating a healthy diet and taking part in physical activity (Section 4.2.3). In participants with a chronic disease, individuals with higher cognitive ability are more likely to adhere to treatment (Section 4.2.4). Section 4.2.5 demonstrated that a possible explanation for the reported phenotypic associations between cognitive ability and health may, in part, be because cognitive ability and health share genetic influences.

The cognitive ability-health associations reported in Section 2.4 are similar to the health literacy-health associations reported in Section 1.4. That is, individuals with limited health literacy and poorer cognitive ability tend to fair worse with regards to health. Despite the similarities between the cognitive ability-health associations and the health literacy-health associations, the research investigating the association between health literacy and health has often not considered the role of cognitive ability, and vice versa. The empirical work reported in this thesis will combine these two areas of research and investigate the associations (both phenotypic and genetic) of health literacy, cognitive ability and health variables. Before detailing the empirical work of this thesis, Chapter 3 will provide an overview of the research to date on the links between health literacy, cognitive ability and health.

3. Health literacy, cognitive ability, and health

Many definitions and theories of health literacy recognise the importance of cognitive ability. For example, Nutbeam (2000) defined health literacy as the "personal, cognitive and social skills" needed to maintain one's health. Paasche-Orlow and Wolf's (2007) model of the pathways linking health literacy and health outcomes proposed that cognitive skills, including memory, reasoning and verbal ability were prerequisites of health literacy. Baker's (2006) model of the associations between individual capacity, health literacy and health identified general knowledge and vocabulary—crystallised abilities—as important antecedents of health literacy. These theories acknowledge that health literacy, and real-life health tasks, are cognitively complex and therefore cognitive ability is a necessary component of health literacy.

3.1. The relationship between health literacy and cognitive ability

Cognitive ability and health literacy are strongly related. Higher scores on cognitive screening tests, such as the MMSE, and more detailed assessments of cognitive ability have been found to be associated with higher scores on tests of health literacy (Baker et al., 2000; Baker et al., 2002; J. S. Bennett, Boyle, James, & Bennett, 2012; Chin et al., 2011; Clouston, Manganello, & Richards, 2017; Dahlke, Curtis, Federman, & Wolf, 2014; Federman, Sano, Wolf, Siu, & Halm, 2009; Murray et al., 2011; Nguyen et al., 2013; Ownby, Acevedo, Waldrop-Valverde, Jacobs, & Caballero, 2014; Wolf et al., 2012). One study (Murray et al., 2011) found that general cognitive ability at age 70 years, created by saving scores on the first unrotated principal component of 6 tests from the WAIS-III, correlated at *rho* = 0.50 with the Newest Vital Sign, *rho* = 0.37 with the S-TOFHLA, and *rho* = 0.37 with the REALM (for all, $p < .001$).

Another study (Federman et al., 2009) found that inadequate scores—defined as scores 1.5 SD or more below age-based norms—on tests of immediate (OR = 3.44, 95% CI 1.71 to 6.94) and delayed (OR = 3.48, 95% CI 1.58 to 7.67) verbal declarative memory, verbal fluency (OR = 3.47, 95% CI 1.44 to 8.38), and on the MMSE (OR = 5.64, 95% CI 2.59 to 12.30) were associated with greater odds of having inadequate health literacy, measured using the S-TOFHLA, even after adjusting for socioeconomic status, and health status (Federman et al., 2009).

Some studies have found different patterns of association between fluid and crystallised ability and different health literacy tests (Chin et al., 2011; Murray et al., 2011; Ownby et al., 2014; Wolf et al., 2012). Using participants from the LBC1936 study, Murray et al. (2011) investigated the association between childhood cognitive ability and relative change in cognitive ability between childhood and older age, with performance on the S-TOFHLA, Newest Vital Sign and REALM. The health literacy tests were measured at age 72 years. A measure of relative cognitive change between age 11 and age 70 years was created by saving the standardised residuals from a linear regression of general cognitive ability measured at 70 years on intelligence test scores measured at age 11 years. In a model controlling for socioeconomic variables and personality traits, both higher scores on an intelligence test at age 11 years ($\beta = 0.35$, $p < .002$) and relatively less steep cognitive change between age 11 and age 70 years ($\beta = 0.24$, $p < .001$) were associated with better performance on the Newest Vital Sign.

Scores on the S-TOFHLA and REALM showed ceiling effects, therefore Murray et al. (2011) used zero-inflated Poisson regression to investigate the association between cognitive ability and the S-TOFHLA and REALM. This regression produces two sets of estimates, one for a hypothetical group of participants whose health literacy scores were less than perfect (“less than mastery”; Murray et al., 2011), and another set estimating the likelihood of perfect health literacy scores (“mastery”; Murray et al., 2011) . When controlling for socioeconomic and personality variables, higher age 11 intelligence test scores (less than mastery coefficient = 0.56, $p < .001$; mastery coefficient = 0.29, $p < .001$; to interpret the effects of these associations, the coefficients need to be exponentiated; Murray et al., 2011), and relatively less steep cognitive change (less than mastery coefficient = 0.58, $p < .001$; mastery coefficient = 0.39, $p < .001$) were associated with both less than mastery and mastery of the S-TOFHLA. Age 11 intelligence predicted less than mastery of the REALM (coefficient = 0.53, $p < .001$), but not mastery of the REALM (coefficient = 0.13, $p > 0.05$). Relative cognitive change was not associated with the REALM (less than mastery coefficient = -0.02; mastery coefficient = 0.36; $p > 0.05$). This suggests that whereas a measure of prior intelligence (crystallised ability) was associated with all three health literacy tests, more fluid abilities that tend to decline across the lifespan were associated with the S-TOFHLA and the Newest Vital Sign, but not the REALM (Murray et al., 2011). The S-TOFHLA and Newest Vital Sign assess more fluid skills such as information processing, whereas the REALM assesses health-related word knowledge (Murray et al., 2011; Ownby et al., 2014).

Health literacy has also been associated with cognitive change over time. Lower scores on tests of health literacy have been found to predict steeper cognitive decline (Yaffe et al., 2009), incidence of mild cognitive impairment (Han, Boyle, James, Yu, & Bennett, 2015) and incidence of dementia (Kaup et al., 2014; Oliveira, Bosco, & di Lorito, 2019; Wilson, Yu, James, Bennett, & Boyle, 2017; Yu, Wilson, Schneider, Bennett, & Boyle, 2017). Participants in the Health, Aging and Body

Composition (Health ABC) study, a prospective cohort study of US community-dwelling adults who were aged 70-79 at baseline, were administered the REALM and were then followed-up for 8 years to determine whether health literacy predicted incidence of “likely” dementia (Kaup et al., 2014). In an unadjusted model, individuals with limited health literacy, compared to those with adequate health literacy, had a 75% increased risk of incident dementia (HR = 1.75; 95% CI 1.44 to 2.13). Even after adjusting for sociodemographic, lifestyle and health variables, and presence of the *APOE* ε4 allele, health literacy remained a significant predictor of incident likely dementia (HR = 1.39; 95% CI 1.04 to 1.85).

3.2. Health literacy as a component of cognitive ability

Given the correlations found between health literacy and cognitive ability, some researchers have proposed that health literacy is not a unique construct, and instead is a component of cognitive ability. Linda Gottfredson (Gottfredson, 2004; Gottfredson & Deary, 2004) proposed that although the contents of health literacy tests are health-specific, these tests are in fact measuring a highly general cognitive ability. Cognitive ability is described as a content- and context-free general ability to learn, reason, and solve problems (Gottfredson, 2004). Although health literacy tests are framed in a health-context, Gottfredson (2004) posits that tests of health literacy are actually measuring a more general ability to learn and problem solve. According to Gottfredson and others (Gottfredson, 2004; Murray et al., 2011), it is this general learning and problem-solving ability, and not domain-specific health skills, that is being applied when completing tests of health literacy and when learning about and managing health.

Reeve and Basalik (2014) set out to formally investigate whether health literacy and cognitive ability where unique constructs, or whether they were measuring the same underlying ability. Reeve and Basalik (2014) recruited 167 participants enrolled in an introductory Psychology course (mean age = 21.31, range 18 to 53) and administered a range of health literacy and cognitive ability tests. Health literacy was assessed with the REALM, S-TOFHLA and Newest Vital Sign. Verbal reasoning, verbal comprehension, numerical ability and numerical reasoning were measured with four scales from the Employee Aptitude Survey (Ruch, Stang, McKillip, & Dye, 2001). The calendar test from the Kit of Factor Referenced Cognitive Tests (Ekstrom, French, Harman, & Derman, 1976) was administered as this test was similar in content to the S-TOFHLA but the questions were not health-related. Finally, a test of reading fluency was administered.

Reeve and Basalik (2014) entered the health literacy tests and the cognitive ability tests into a factor analysis to determine whether a unique health literacy construct emerged. For this factor analysis, scores on S-TOFHLA Reading and Numeracy sections were entered separately. Three factors emerged, which accounted for 59% of the variance. A unique health literacy factor did not emerge. In fact, the three health literacy measures each loaded on different cognitive factors (Reeve & Basalik, 2014). According to Reeve and Basalik (2014), the first factor reflected general reasoning ability and tests of numerical reasoning (loading = 0.88), numerical ability (0.68), verbal reasoning (0.51) and the Newest Vital Sign (0.31) loaded on this factor. The second factor reflected verbal ability and the REALM (0.79), reading fluency (0.96), and verbal comprehension (0.45) loaded on this factor. The final factor was thought to reflect visual scanning and the Newest Vital Sign (0.30), S-TOFHLA Numeracy (0.68), and the calendar task (0.41) loaded on this factor. Based on their findings that no unique health literacy factor emerged, Reeve and Basalik (2014) concluded that tests of functional health literacy and cognitive ability are measuring the same underlying abilities.

3.3. The role of cognitive ability in the association between age and health literacy

If cognitive ability and health literacy are measuring the same underlying ability, then one would expect previously reported associations between health literacy and outcomes such as age and health to be attenuated when also adjusting for cognitive ability. Cognitive ability has been found to attenuate the relationship between lower health literacy and older age (Baker et al., 2000; Boyle et al., 2013; Kaphingst, Goodman, MacMillan, Carpenter, & Griffey, 2014; Kobayashi et al., 2015). Baker et al. (2000) examined the association between the S-TOFHLA and age, with and without adjusting for cognitive ability, in a sample of US adults aged over 65 years. Controlling for sex, race, ethnicity, and education, but not MMSE score, the S-TOFHLA score was 1.3 (SE = 0.1, $p < .001$) points lower for every year increase in age (Baker et al., 2000). Additionally, adjusting for MMSE scores attenuated this association by 31%; however, S-TOFHLA scores were still associated with age (beta = -0.9, SE = 0.1, $p < .001$). As detailed in Section 2.2.2, the MMSE is only a crude measure of cognitive function and does not comprehensively measure all aspects of cognitive ability.

Using more detailed tests of cognitive ability, Kobayashi et al. (2015) investigated the role of fluid and crystallised ability in the association between age and health literacy in a sample of 828 adults aged 55-74 years. In this cross-sectional study, participants completed a battery of 16 cognitive tests and the TOFHLA, REALM and Newest Vital Sign. Latent measures of fluid and crystallised ability were derived from scores on the cognitive tests. In models with only age entered, older participants had poorer scores on the TOFHLA and Newest Vital Sign, however REALM scores did not differ as a function of age. Adding crystallised ability to the model did not attenuate the association between age and TOFHLA and Newest Vital Sign; however, adding fluid ability to the model attenuated the age-TOFHLA association by 85% and the age-Newest Vital Sign association by 68% (Kobayashi et al., 2015). The often-reported association between health literacy and age may reflect the fact that some measures of health literacy, such as the TOFHLA and Newest Vital Sign, are tapping fluid abilities, which decline in age (Kobayashi et al., 2015).

3.4. The role of cognitive ability in the association between health literacy and health

Given the wealth of evidence linking health literacy to health outcomes, and the finding that health literacy and cognitive ability tests are strongly correlated, researchers have begun to examine the role of cognitive ability in the association between health literacy and health (Baker, Wolf, Feinglass, & Thompson, 2008; Bostock & Steptoe, 2012; Kobayashi, Wardle, Wolf, & von Wagner, 2016b; Lamar et al., 2019; Mõttus et al., 2014; O'Conor et al., 2015; Serper et al., 2014; Wolf et al., 2012). Most studies find that cognitive ability accounts for a large portion of the association between health literacy and health; however, the degree of attenuation varies. Some studies find that health literacy is no longer associated with health when also measuring cognitive ability (O'Conor et al., 2015; Serper et al., 2014; Wolf et al., 2012). One study (O'Conor et al., 2015) investigated the role of health literacy and cognitive ability in three aspects of asthma management—asthma medication adherence, metered-dose inhaler technique, and dry powder inhaler technique—in 425 older adults with asthma. Health literacy was measured using the S-TOFHLA. Measures of fluid and crystallised ability were created based on scores on six cognitive tests assessing a range of different cognitive domains. When adjusting for demographic and health variables, adequate compared to limited health literacy was associated with better adherence, measured by scoring ≥ 4.5 on the 10 item Medication Adherence Reporting Scale (OR = 2.30, 95% CI 1.29 to 4.08); better metered-dose inhaler technique, measured by correctly completing > 75% of 7 defined steps when demonstrating the use of a metered-dose inhaler (OR = 1.64, 95% CI 1.01 to 2.65); and better dry powder inhaler technique, measured by correctly completing > 75% of 8 steps when demonstrating the use of a dry-powder inhaler (OR = 3.51, 95% CI 1.81 to 6.83). Adjusting for fluid and crystallised ability attenuated these associations by 37% for adherence (OR = 1.45, 95% CI 0.70 to 2.98), 34% for metered-dose inhaler technique (OR = 1.09, 95% CI 0.59 to 2.02), and 46% for dry powder inhaler technique (OR = 1.89, 95% CI 0.82 to 4.39), respectively, and health literacy was no longer associated with these asthma management behaviours (O'Conor et al., 2015).

Using 730 participants from the LBC1936 study, Mõttus et al. (2014) tested whether childhood and older age cognitive ability attenuated any assocation between health literacy and physical health. Whereas cognitive ability fully attenuated the assocation between health literacy and some aspects of physical health, for other assocaitons, the relationship between health literacy and physical health remained, though was attenuated, after adjustment for cognitive ability (Mõttus et al., 2014). In models without cognitive ability, a 1 SD higher health literacy score—created by entering test scores on the S-TOFHLA, REALM and Newest Vital Sign into a confirmatory factor analysis and saving the factor score—was associated with better physical fitness (created by saving the first unrotated principcal component from a

PCA of 6 meter walk time, grip strength, and forced expiratory volumne in 1 second; β = 0.160, SE = 0.025, $p < .001$), a lower BMI (β = -0.077, SE = 0.037, $p < .05$) and a higher number of natural teeth (β = 0.197, SE = 0.039, $p < .001$). Adjusting for general cognitive ability in older age significantly attenuated the assocation between health literacy and physical fitness by 43% (β = 0.093, SE = 0.030, $p < 0.01$) and number of natural teeth by 39% (β = 0.120, SE = 0.048, $p < 0.05$), but it did not attenuate the assocation between health literacy and BMI (β = -0.053, SE = 0.047, $p > .05$). Adjusting for childhood cognitive ability did not attenuate the assocaiton between health literacy and physical fitness (β = 0.160, SE = 0.030, $p < .001$), but childhood cognitive ability attenuated the assocaiton between health literacy and BMI by 88% (β = -0.009, SE = 0.045, $p > .05$), and number of natural teeth by 39% (β = 0.138, SE = 0.046, $p < .01$).

Other studies have found that, although the size of the association between health literacy and health is reduced when adjusting for cognitive ability, health literacy is still uniquely associated with health independent of cognitive ability (Baker et al., 2008; Bostock & Steptoe, 2012; Kobayashi et al., 2016b). Bostock and Steptoe (2012) found that whereas the risk of mortality for individuals with low compared to high health literacy reduced from 41% (15% to 73%) to 26% (3% to 56%) when additionally adjusting for brief tests of cognitive ability, health literacy remained a unique contributor to mortality. However, the authors (Bostock & Steptoe, 2012) only adjusted for orientation in time (correctly stating the day of the week, date, month and year), immediate recall of 10 words, and number of animals named in 60 seconds. It is possible that health literacy remained significantly associated with mortality when adjusting for cognitive ability because only a small number of brief tests of cognitive ability were used that may not be adequately capturing sufficient variance in general cognitive ability.

A recent study, however, found that some health literacy-health associations do not change, even after adjusting for a very detailed measure of cognitive ability. Lamar et al. (2019) investigated the association between health literacy, cognitive ability and diabetes indicators in a sample of 908 Rush Memory and Aging Project participants with and without a reported diagnosis of diabetes. Adjusting for demographic variables, a one percentage increase in scores on a 9-question health literacy test was associated with a 0.005 (SE = 0.001, p = .0007) lower value in HbA1c levels. Additionally adjusting for a global measure of cognitive ability, created using scores from 19 well-validated cognitive tests, as well as diabetes status, hypertension status, and depressive symptoms, did not change the association between health literacy and HbA1c levels (beta = -0.005, SE = 0.001, p = .00005). In this model, global cognitive function was not associated with HbA1c levels (beta per one SD increase in global cognitive function = −0.01, SE = 0.04, p = .71). This study (Lamar et al., 2019) also examined the association between health literacy and blood glucose levels (mg/dL) and again found that cognitive ability did not attenuate the association. The size of the association between health literacy and blood glucose levels (beta = -0.21, SE = 0.09, p = .01) changed only slightly when additionally adjusting for cognitive ability and health variables (beta = -0.19, SE = 0.09, p = .03).

With the exception of the study by Lamar et al. (2019), the literature reviewed in this section shows that cognitive ability at least partly attenuates the previously-reported associations between health literacy and health. However, the degree of attenuation varies between studies. If, as Reeve and Basalik (2014) proposed, health literacy and cognitive ability are measuring the same underlying construct, one would expect to find that cognitive ability, if assessed comprehensively, entirely attenuates any association between health literacy and health. However, this is not always what is reported. Some studies have found that both health literacy and cognitive ability uniquely contribute to health (Baker et al., 2008; Bostock & Steptoe, 2012; Kobayashi et al., 2016b). These studies tended to use relatively brief cognitive assessments, such as the MMSE or short cognitive tests and therefore it is possible that health literacy independently contributed to health in these studies because of residual cognitive capability not picked up by the brief cognitive assessments used. However, the cognitive ability measure used in Lamar et al. (2019), which consisted of a composite score based on performance of 19 cognitive tests, was comprehensive. Yet, adjusting for this score did not change the association between health literacy and diabetes indicators.

Studies investigating the role of cognitive ability in the association between health literacy and health have examined a range of different health outcomes, including health behaviours (Kobyashi et al., 2016), disease management (O'Conor et al., 2015), physical health (Mõttus et al., 2014), and death (Bostock & Steptoe, 2012). It is possible that the contributions of health literacy and cognitive ability to health may be different depending on the health outcome assessed. The empirical work carried out in this thesis will investigate the associations of cognitive ability and health literacy with a range of different health outcomes, including health behaviours, risk of chronic disease, and death.

3.5. Summary and aims of this thesis

Chapter 3 has shown that health literacy and cognitive ability are strongly correlated and that there is likely an overlap in the ability (or abilities) assessed with tests of cognitive ability and health literacy. There is a wealth of research that has investigated the association between health literacy and various aspects of health

(Section 1.4) and a separate body of literature showing that cognitive ability is associated with many health outcomes (Section 2.4). A relatively small body of research has concurrently examined health literacy and cognitive ability and their association with health (Section 3.4). Those that have done so have generally found that the association between health literacy and health is attenuated when adjusting for cognitive ability. Whereas some have found that cognitive ability almost entirely attenuates the association between health literacy and health, others have found that both health literacy and cognitive ability account for unique variance in health outcomes. It is possible that differences in results may be due to different cognitive and health literacy assessments used, or possibly that health literacy and cognitive ability have different patterns of associations with different health outcomes.

The aim of this thesis was to expand on the work reported in Chapter 3 and examine the associations of both health literacy and cognitive ability in health. A secondary aim was to advance the work carried out by Reeve and Basalik (2014) and investigate the overlap between cognitive ability and health literacy. Specifically, the aims of the empirical work reported in this thesis were:

- **Main aim:** To investigate the unique contributions of health literacy and cognitive ability to aspects of health.
- **Secondary aim:** To investigate further the association between health literacy and cognitive ability.

Cognitive ability and health literacy have separately been found to be associated with many aspects of health, including morbidity, mortality, disease management, and even disease prevention. This thesis investigates the unique associations of health literacy and cognitive ability, when studied separately and together, in various aspects of health, including health behaviours, chronic disease, and mortality. In addition to examining the phenotypic associations between health literacy and cognitive ability with health, this thesis will also test the genetic associations of health literacy, cognitive ability and health. Whereas the genetic associations of cognitive ability, and the genetic correlations between cognitive ability and health have been investigated (Section 2.4.5), no research has been carried out examining the genetic architecture of health literacy, and the genetic overlap between health literacy with cognitive ability and health. Therefore, to better understand the relationship these three variables, this thesis will examine both the phenotypic and genetic associations of health literacy, cognitive ability, and health.

The empirical work reported in Chapter 4 investigates the associations of health literacy and cognitive ability in a health risk behaviour: smoking status. This chapter investigates whether health literacy and cognitive ability are independently associated with whether individuals have ever smoked, and in ever smokers, it additionally investigates whether they continue to smoke or have quit. The association of health literacy and cognitive ability, when examined individually and concurrently, in risk of developing a common chronic disease—diabetes—is investigated in Chapter 5. The empirical work reported in Chapter 6 investigates whether health literacy in older age is associated with risk of all-cause mortality, and tests whether this association remains when additionally accounting for childhood cognitive ability and cognitive ability measured in older adulthood. A study exploring the genetic contributions to health literacy is reported in Chapter 7. Among other genetic analyses, using polygenic profile scoring, this study tests whether common genetic variants previously found to be associated with cognitive and health-related traits are associated with performance on a test of health literacy.

4. Health literacy, cognitive ability, and smoking

4.1. Introduction

An important aspect of good health and disease prevention is participating in health-promoting behaviours, such as eating a healthy diet, taking part in regular physical activity, and not smoking. Section 1.4.3 detailed that the evidence for an association between higher health literacy and being more likely to take part in health promoting behaviours is mixed. Whereas some studies have found that higher health literacy scores are associated with participating in healthy behaviours, such as higher fruit and vegetable intake and not smoking (von Wagner et al., 2007), others have not (Wolf et al., 2007). As outlined in Section 2.4.3, a number of studies have shown that individuals with higher cognitive ability are more likely to take part in a range of healthy behaviours, including being more likely to exercise regularly, eat foods thought to be food for you, maintain a healthy weight, and report never smoking, or, in ever smokers, that they have quit smoking (Batty, Deary, & Macintyre, 2007; Batty, Deary, et al., 2007a, 2007b; Hemmingsson et al., 2008; M. D. Taylor et al., 2003; Wraw et al., 2018).

The role of health literacy and cognitive ability in taking part in health promoting behaviours, when studied together, is not well understood. Using 4,345 participants from ELSA, one study (Kobayashi et al., 2016b) investigated the relationship between health literacy and physical activity before and after adjusting for brief tests of cognitive ability. Health literacy was assessed using a brief, 4-item test of functional health literacy (described in Section 1.4.2). Scores on the health literacy test were categorised as high (4/4 correct), medium (3/4 correct), or low (less than 3 correct). The outcome variable was whether participants consistently reported taking part moderate-to-vigorous physical activity at least once per week at 5 ELSA assessments over an 8-year period (Kobayashi et al., 2016b). Controlling for sociodemographic and health status variables, compared to those with low health literacy, those with high health literacy were 53% (OR = 1.53, 95% CI 1.16 to 2.01) more likely to report consistently taking part in moderate-to-vigorous physical activity. Next, Kobayashi et al. (2016b) sought to quantify the attenuation in the association between health literacy and physical activity when additionally adjusting for cognitive ability. A composite memory measure (maximum score = 24) was created by summing scores on a 4-item test of orientation in time, immediate recall of 10 words, and delayed recall of 10 words. Verbal fluency was assessed by asking participants to name as many animals as possible in 60 seconds. Scores on the verbal fluency test were divided into 10 categorises and scored from 0 to 9, with higher scores reflecting better performance. The association between health literacy and physical activity was attenuated by 30% (OR = 1.37, 95% CI 1.04 to 1.81) when additionally adjusting for the composite memory measure and verbal fluency; however, health literacy remained a significant predictor of regular physical activity (Kobayashi et al., 2016b). There were also small associations between higher verbal fluency (OR per point increase = 1.05, 95% CI 1.01 to 1.09) and memory (OR per point increase = 1.03, 95% CI 1.00 to 1.05) scores with consistently taking part in physical activity. Thus, both health literacy and cognitive ability were independently associated with consistently participating in physical activity over an 8 year period (Kobayashi et al., 2016b).

The unique contributions of health literacy and cognitive ability with other health behaviours has not been investigated. Using participants from ELSA—the same sample as used in Kobayashi et al. (2016b)—the present chapter examines whether health literacy and cognitive ability are associated with another health behaviour;

smoking status. It is well reported that smoking is associated with increased morbidity and mortality (Allender, Balakrishnan, Scarborough, Webster, & Rayner, 2009). Despite the health warnings, one in seven people in the UK continue to smoke (Office for National Statistics, 2017). Using a more detailed measure of cognitive ability than was used in Kobayashi et al. (2016b), the present cross-sectional study investigated whether health literacy and cognitive ability, when studied individually and concurrently, are associated with whether a sample of middle-aged and older ELSA participants reported ever smoking, and, in ever smokers, whether they reported smoking nowadays. This study has been published in *BMJ Open,* and the published paper is included in Section 4.2.

4.2. Health literacy, cognitive ability and smoking: a cross-sectional analysis of the English Longitudinal Study of Ageing

BMJ Open

Health literacy, cognitive ability and smoking: a cross-sectional analysis of the English Longitudinal Study of Ageing

Chloe Fawns-Ritchie,[1,2] John M Starr,[1,3] Ian J Deary[1,2]

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[1]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
[2]Department of Psychology, University of Edinburgh, Edinburgh, UK
[3]Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK

Correspondence to
Professor Ian J Deary; ian.deary@ed.ac.uk

ABSTRACT

Objectives We used logistic regression to investigate whether health literacy and cognitive ability independently predicted whether participants have ever smoked and, in ever smokers, whether participants still smoked nowadays.

Design Cross-sectional study.

Setting This study used data from Wave 2 (2004–05) of the English Longitudinal Study of Ageing, which is a cohort study of adults who live in England and who, at baseline, were aged 50 years and older.

Participants 8734 (mean age=65.31 years, SD=10.18) English Longitudinal Study of Ageing participants who answered questions about their current and past smoking status, and completed cognitive ability and health literacy tests at Wave 2.

Primary and secondary outcome measures The primary outcome measures were whether participants reported ever smoking at Wave 2 and whether ever smokers reported still smoking at Wave 2.

Results In models adjusting for age, sex, age left full-time education and occupational social class, limited health literacy (OR=1.096, 95% CI 0.988 to 1.216) and higher general cognitive ability (OR=1.000, 95% CI 0.945 to 1.057) were not associated with reporting ever smoking. In ever smokers, limited compared with adequate health literacy was associated with greater odds of being a current smoker (OR=1.194, 95% CI 1.034 to 1.378) and a 1 SD higher general cognitive ability score was associated with reduced odds of being a current smoker (OR=0.878, 95% CI 0.810 to 0.951), when adjusting for age, sex, age left full-time education and occupational social class.

Conclusions When adjusting for education and occupation variables, this study found that health literacy and cognitive ability were independently associated with whether ever smokers continued to smoke nowadays, but not with whether participants had ever smoked.

Strengths and limitations of this study

- This study used a large sample (n=8734) from the English Longitudinal Study of Ageing, a study designed to be representative of the English population aged over 50 years.
- This analysis was cross-sectional and therefore cannot determine the direction of the association between smoking, health literacy and cognitive ability.
- This study included measures of both health literacy and cognitive ability which allowed us to investigate whether health literacy was associated with smoking status when controlling for cognitive ability.
- Smoking status was self-reported.

INTRODUCTION

The effects of smoking on ill health have been known for decades. The prevalence of smoking in the UK is falling and the number of smokers who are quitting is increasing.[1] Despite this, nearly 16% of the UK population were current smokers in 2016[1] and smoking remains one the largest causes of preventable morbidity and mortality in the UK.[1 2] Understanding the characteristics of individuals who take up smoking and who quit smoking is important to be able to design and target smoking education and interventions.

Cognitive ability is associated with smoking. Individuals who smoke have lower scores on cognitive tests than those who have never smoked.[3–5] Smokers show steeper ageing-related cognitive decline[4–7] and have increased risk of Alzheimer's disease,[6 8] compared with non-smokers. One possible pathway between smoking and cognitive ability is that smoking has harmful consequences for the vascular system, which could in turn affect cognitive functioning.[6 9]

A perhaps complementary explanation is that individuals who have lower cognitive ability in youth are more likely to take up smoking and less likely to quit.[9–11] Corley *et al*[9] found that, when controlling for childhood cognitive ability, the association between smoking and cognitive function in old age was attenuated and, in some cases, became non-significant. Two studies[10 12] found different patterns when investigating the relationship between childhood cognitive ability and reporting ever smoking. One study using the 1970 British Birth Cohort[10] found that individuals with higher childhood cognitive ability were less likely to have ever smoked in a sample of middle-aged participants, whereas another report, based on two of the Midspan prospective cohort studies,[12] found no association between cognitive ability in childhood and ever smoking in a sample of older adults. Both these studies, however, found that among ever smokers, individuals with higher childhood cognitive ability were more likely to quit smoking.[10 12]

A person's health literacy may also play a role in smoking status, though the evidence for an association between health literacy and smoking is mixed.[13–16] Health literacy is the capacity to acquire, process and use health information to successfully navigate all aspects of health, including the ability to use health documents, interact with healthcare professionals and undertake health-promoting behaviours to prevent future ill health.[17 18] Some studies have found that individuals with lower health literacy are more likely to smoke,[13 14] whereas others have not.[15 16] It is possible that individuals who have limited health literacy are less aware of the adverse effects of smoking on health, and may be less able to understand and use smoking cessation services.

The current study sought to determine whether health literacy and cognitive ability, when studied together, have independent associations with smoking. Drawing on the English Longitudinal Study of Ageing (ELSA), we first investigated whether health literacy and cognitive ability were independently associated with whether individuals had ever smoked. Second, we investigated whether there was a relationship between health literacy, cognitive ability and whether ever smokers continued to smoke, or quit.

METHODS

Participants

This study used data from ELSA, a panel study designed to be representative of individuals aged 50 years and older living in England.[19] A total of 11 391 participants took part in Wave 1 in 2002–2003. Wave 1 participants were individuals who had previously taken part in the Health Survey for England, were born before 1 March 1952 and were living in a private household in England at the first wave.[19] These participants have been followed up every 2 years, and the sample has been refreshed at subsequent waves to maintain a representative sample of participants aged over 50 years. More information on this cohort is provided elsewhere.[19] The current sample consists of participants who completed the Wave 2 (2004–2005) interview (n=8780); this is the first wave in which health literacy was assessed. Ethical approval was granted. This study conformed to the principles embodied in the Declaration of Helsinki.

Measures

ELSA interviews were carried out using computer-assisted interviewing in the participants' own home.

Smoking

Two aspects of smoking status (ever vs never smoker and current vs former smoker) were the outcome variables in these analyses. Participants were asked 'Have you ever smoked cigarettes?'. Participants were categorised as ever smokers if they answered 'yes' and never smokers if they answered 'no' at either Wave 1 or 2. Ever smokers were additionally asked 'Do you smoke cigarettes at all nowadays?'. Ever smokers who answered 'yes' to smoking cigarettes nowadays at Wave 2 were categorised as current smokers, whereas ever smokers who answered 'no' were categorised as former smokers.

Health literacy

Health literacy was assessed at Wave 2 using a four-item comprehension test previously used in the International Adult Literacy Survey.[20] Participants were presented with a piece of paper containing instructions similar to those that would be found on a packet of over-the-counter medication. Participants were instructed to read the medicine label and were then asked four questions about the information on this label (eg, 'what is the maximum number of days you may take this medicine?'). The label was available to the participant to refer to at any time. This task was designed to measure the skills thought to be required to understand and use health materials correctly, such as the ability to read and use numbers in a health context.[21] One point was awarded for each correctly answered question (range 0–4). As has been done in previous ELSA studies,[22 23] health literacy scores were categorised as 'adequate' (4/4 correct) or 'limited' (≤3 correct).

Cognitive function

Four tests of cognitive function that were administered at Wave 2 of the ELSA study were used here. These tests are thought to assess episodic memory, executive function and processing speed; these are cognitive domains which tend to decline on average with increasing age.[24 25] In the word list recall test, participants heard a list of 10 words which they had to recall immediately (immediate recall test) and again after a short delay (delayed recall test). The score on each occasion was the number of words remembered (range 0–10). Executive function was assessed using categorical verbal fluency (number of animals named in 60 s). The letter cancellation test, in which participants were to scan rows of letters and score out all Ps and Ws, was used to measure processing speed. The score is the number of Ps and Ws scored out in 60 s. Exploratory factor analysis (EFA) using principal axis factoring was used to derive a composite measure of general cognitive ability. Scores on the four cognitive tests were entered into the EFA. Prior to this, individuals who scored 0 or greater than 4 SD above the mean on the animal fluency test and the letter cancellation test were removed. Scores of 0 indicate that the participant did not understand the task, and scores 4 SD above the mean were seen as dubiously high given the 1 min time limit for these tests. One unrotated factor was extracted which accounted for 44% of the total variance in the four cognitive tests. The loadings of the tests were: immediate word recall=0.78; delayed word recall=0.83; animal naming=0.53; letter cancellation=0.42. This factor score was converted to a z-score (mean=0.00, SD=1.00) and was used as a measure of general cognitive ability.

Covariates

Age in years, sex, age of leaving full-time education and occupational social class were used as covariates. For confidential reasons, owing to there being few of them, participants aged over 90 years have had their age set to 90. Participants were asked at what age they left continuous full-time education (recorded as not yet finished, never went to school, 14 or under, at 15, at 16, at 17, at 18, and 19 or over). For the purpose of this study, age of leaving full-time education was categorised as 14 years or under, 15–16 years, 17–18 years and 19 years or over. Occupational social class was categorised using the National Statistics Socio-economic Classification 3 categories: managerial and professional, intermediate and routine and manual.[26]

Patient and public involvement

Participants were not involved in the development of any part of this study.

Statistical analysis

Two sets of analyses were carried out. First, ever smokers were compared with never smokers; second, current smokers were compared with former smokers. To determine whether ever versus never smokers and current versus former smokers differ on health literacy, general cognitive ability and sociodemographic variables, t-tests were used for normally distributed continuous variables, Mann-Whitney U tests were used for non-normal continuous variables and χ^2 tests were used for categorical variables. Rank-order correlations were calculated between the predictor variables to examine any bivariate associations between these variables. Binary logistic regression was used to examine the independent associations of health literacy and general cognitive ability on smoking status. Age and sex were entered in all models. Health literacy and general cognitive ability were entered individually in models 1 and 2, respectively. To determine whether both health literacy and general cognitive ability are independently associated with smoking, both predictors were included in model 3. Model 4 additionally adjusted for age of finishing full-time education and occupational social class to determine whether any associations between health literacy, cognitive function and smoking remained after controlling for these sociodemographic variables.

RESULTS

Of the 8780 participants who completed the Wave 2 interview, 8734 participants had complete data on smoking, cognitive ability and health literacy, and they make up the analytic sample. Participant characteristics are reported in table 1. A total of 5525 (63.3%) participants reported ever smoking, whereas 3209 (36.7%) participants reported having never smoked. Ever smokers were more likely to have limited health literacy and have a lower general cognitive ability than never smokers. Ever smokers were older, were more likely to be male, have left full-time education at a younger age and have a lower occupational social class than never smokers. A total of 1356 (15.5%) participants reported that they still smoked cigarettes at Wave 2, whereas 4169 (47.7%) participants reported that they had stopped. Current smokers were more likely to have limited health literacy than former smokers; however, the two groups did not differ on general cognitive ability. Current smokers were younger, more likely to be female, have left full-time education at a younger age and to have a lower occupational social class than former smokers. Given that current smokers were, on average, 4.5 years younger than former smokers, we tested the point-biserial correlation between smoking status and general cognitive ability, with and without controlling for age. When not controlling for age, the correlation between smoking and general cognitive ability was 0.01 (p=0.389). Adjusting for age, the correlation was −0.09 and this was significant (p<0.001).

Rank-order correlations between the predictor variables are shown in table 2. All predictor variables were significantly correlated with each other, with the exception of sex with health literacy and education. Having adequate health literacy was moderately associated with having higher general cognitive ability (r=0.31, p<0.001). Adequate health literacy was associated with having higher qualifications (r=0.23, p<0.001) and a higher occupational class (r=−0.18, p<0.001). Older adults were less likely to have adequate health literacy (r=−0.16, p<0.001). General cognitive ability was strongly correlated with age. Older individuals tended to have lower general cognitive ability (r=−0.46, p<0.001). Female participants (r=−0.10, p<0.001), individuals with higher qualifications (r=0.38, p<0.001) and higher occupational class (r=−0.25, P<0.001) tended to have higher general cognitive ability.

Table 3 shows the ORs and 95% CIs for reporting ever smoking. Adjusting for age and sex only, limited health literacy was associated with greater odds of ever smoking (model 1 OR=1.174, 95% CI 1.067 to 1.293). A 1 SD higher score in general cognitive ability was associated with an 8.1% reduction in reporting ever smoking (model 2 OR=0.919, 95% CI 0.874 to 0.967). The associations between health literacy and general cognitive ability with ever smoking remained significant, though slightly reduced in size, in the model including both health literacy and cognitive ability (model 3). In model 4, which additionally adjusted for sociodemographic variables, the associations between health literacy (OR=1.096, 95% CI

Table 1 Participant characteristics according to smoking status (n=8734)*

	Smoking history			Smoking cessation†		
	Ever smoker (n=5525)	**Never smoker (n=3209)**	**P values for difference**	**Current smoker (n=1356)**	**Former smoker (n=4169)**	**P values for difference**
Health literacy, n (%)			0.001			<0.001
Adequate	3647 (66.0)	2233 (69.6)		840 (61.9)	2807 (67.3)	
Limited	1878 (34.0)	976 (30.4)		516 (38.1)	1362 (32.7)	
General cognitive ability, mean (SD)	−0.04 (1.00)	0.08 (0.99)	<0.001	−0.02 (0.99)	−0.05 (1.01)	0.385
Age (years), mean (SD)	65.53 (10.13)	64.93 (10.24)	0.005	62.12 (9.12)	66.64 (10.20)	<0.001
Sex, n (%)			0.001			<0.001
Female	2752 (49.8)	2172 (67.7)		761 (56.1)	1991 (47.8)	
Male	2773 (50.2)	1037 (32.3)		595 (43.9)	2178 (52.2)	
Age left full-time education, n (%)			<0.001			<0.001
14 years or under	1104 (20.6)	553 (17.6)		233 (17.7)	871 (21.5)	
15–16 years	2936 (54.8)	1578 (50.2)		856 (65.0)	2080 (51.4)	
17–18 years	665 (12.4)	488 (15.5)		128 (9.7)	537 (13.3)	
19 years or over	657 (12.3)	526 (16.7)		99 (7.5)	558 (13.8)	
Occupational social class, n (%)			<0.001			<0.001
Managerial and professional	1677 (30.8)	1047 (33.2)		274 (20.6)	1403 (34.2)	
Intermediate	1263 (23.2)	884 (28.1)		312 (23.4)	951 (23.2)	
Routine and manual	2499 (45.9)	1218 (38.7)		747 (56.0)	1752 (42.7)	

*Characteristics for age left full-time education are based on a subset of 8507 participants with this data and characteristics for occupational social class are based on a subset of 8588 participants with this data.
†For smoking cessation comparisons, the ever smoker category is divided into whether ever smokers are current or former smokers.

0.988 to 1.216) and general cognitive ability (OR=1.000, 95% CI 0.945 to 1.057) with ever smoking were partly and fully attenuated, respectively, and no longer significant.

The ORs (95% CIs) for whether ever smokers reported being a current smoker at Wave 2 are shown in table 4. For this analysis, a Box-Tidwell test revealed that models violated the assumption of linearity of the logit; therefore, an age-squared term was included in these models. To overcome multicollinearity, the ORs and CIs are based on models using centred continuous variables. Controlling for age and sex only, having limited health literacy compared with adequate health literacy was associated with 49.3% greater odds of being a current smoker (model 1 OR=1.493, 95% CI 1.307 to 1.704). A 1 SD higher score in general cognitive ability was associated with 22.8% lower odds of reporting being a current smoker (model 2

Table 2 Rank-order correlations between predictor variables (pairwise n=8367–8734)

	Health literacy	**General cognitive ability**	**Age (years)**	**Sex**	**Education**	**Occupational class**
Health literacy	–					
General cognitive ability	0.31***	–				
Age (years)	−0.16***	−0.46***	–			
Sex	0.01	−0.10***	0.02*	–		
Education	0.23***	0.38***	−0.40***	0.00	–	
Occupational class	−0.18***	−0.25***	0.07***	−0.09***	−0.41***	–

*p<0.05, **p<0.01, ***p<0.001.
Health literacy was coded 0 for inadequate health literacy, 1 for adequate health literacy; sex was coded 0 for women, 1 for men; education is age left full-time education and was coded 1 for 14 years or under, 2 for 15–16 years, 3 for 17–18 years, 4 for 19 years or older; occupational social class was coded 1 for managerial and professional, 2 for intermediate, 3 for routine and manual.

Table 3 ORs and 95% CIs from logistic regression models of whether participants have ever smoked

	Model 1 (n=8734)	Model 2 (n=8734)	Model 3 (n=8734)	Model 4 (n=8367)
Health literacy				
Adequate	Reference	Reference	Reference	Reference
Limited	1.174 (1.067 to 1.293)**	–	1.134 (1.026 to 1.254)*	1.096 (0.988 to 1.216)
General cognitive ability†	–	0.919 (0.874 to 0.967)**	0.936 (0.888 to 0.987)*	1.000 (0.945 to 1.057)
Age (years)	1.004 (1.000 to 1.008)	1.001 (0.996 to 1.006)	1.001 (0.996 to 1.006)	1.002 (0.996 to 1.007)
Sex				
Female	Reference	Reference	Reference	Reference
Male	2.112 (1.929 to 2.313)***	2.077 (1.896 to 2.276)***	2.087 (1.905 to 2.288)***	2.150 (1.955 to 2.366)***
Age left full-time education				
14 years or under	–	–	–	Reference
15–16 years	–	–	–	1.016 (0.880 to 1.172)
17–18 years	–	–	–	0.828 (0.690 to 0.994)*
19 years or older	–	–	–	0.693 (0.572 to 0.839)***
Occupational class				
Managerial and professional	–	–	–	Reference
Intermediate	–	–	–	0.919 (0.810 to 1.041)
Routine and manual	–	–	–	1.204 (1.066 to 1.360)**

*p<0.05, **p<0.01, ***p<0.001.
†ORs (95% CIs) for general cognitive ability are the odds of reporting ever smoking for a 1 SD increase in general cognitive ability.

OR=0.772, 95% CI 0.718 to 0.829). Including both health literacy and general cognitive ability in model 3 reduced the size of the associations, but they remained significant. These associations continued to remain significant, though further attenuated, in the fully adjusted model, which additionally adjusted for age completed full-time education and occupational social class (model 4 OR for limited compared with adequate health literacy=1.194, 95% CI 1.034 to 1.378; OR for a 1 SD higher score in general cognitive ability=0.878, 95% CI 0.810 to 0.951). In this final model, age left full-time education and occupational social class were also significantly associated with reporting being a current smoker. Compared with individuals who left full-time education at 14 years or under, those who left at age 17–18 or over 19 years had reduced odds of being a current smoker. Compared with those with a managerial or professional occupational class, those with a routine or manual occupational class had increased odds of being a current smoker.

DISCUSSION

This study found that in a sample of middle-aged and older adults residing in England, health literacy and cognitive ability were independently related with whether ever smokers continue to smoke nowadays, but not with whether individuals have ever smoked. Adjusting for age and sex only, participants with limited health literacy and lower cognitive ability were more likely to report having ever smoked. However, when additionally adjusting for age left full-time education and occupational class, these associations were attenuated and became non-significant. This suggests that health literacy and cognitive function do not have associations with ever smoking that are independent of education and occupational class. In ever smokers, those with limited health literacy and poorer cognitive ability were more likely to report that they continued to smoke. These associations remained, though slightly attenuated, even after adjusting for measures of socioeconomic status.

Whereas previous studies have found associations between health literacy and smoking,[13 14] and cognitive ability and smoking,[3–10 12] to the best of our knowledge, this is the first study to find that both health literacy and cognitive function are independently associated with smoking cessation. Health literacy and cognitive function are strongly related[27–30] and some have proposed that health literacy is not a unique construct and is, rather, a subcomponent of general cognitive ability.[30] The current study, however, found that both health literacy and cognitive ability each play independent roles in predicting smoking cessation which is in support of health literacy and cognitive ability being separate, although related, constructs.

A particularly important finding from the current study was that health literacy, independent of cognitive ability, education and occupational social class, was associated with whether ever smokers continued to smoke.

Table 4 ORs and 95% CIs from logistic regression models of whether ever smokers still smoke nowadays

	Model 1 (n=5525)	Model 2 (n=5525)	Model 3 (n=5525)	Model 4 (n=5280)
Health literacy				
Adequate	Reference	Reference	Reference	Reference
Limited	1.493 (1.307 to 1.704)***	–	1.338 (1.165 to 1.536)***	1.194 (1.034 to 1.378)*
General cognitive ability†	–	0.772 (0.718 to 0.829)***	0.805 (0.747 to 0.868)***	0.878 (0.810 to 0.951)**
Age	0.952 (0.945 to 0.958)***	0.943 (0.936 to 0.951)***	0.943 (0.936 to 0.950)***	0.938 (0.929 to 0.947)***
Age^2	0.999 (0.999 to 1.000)**	0.999 (0.999 to 1.000)**	0.999 (0.999 to 1.000)**	0.999 (0.998 to 1.000)**
Sex				
Female	Reference	Reference	Reference	Reference
Male	0.744 (0.655 to 0.845)***	0.707 (0.622 to 0.803)***	0.714 (0.628 to 0.811)***	0.755 (0.661 to 0.863)***
Age left full-time education				
14 years or under	–	–	–	Reference
15–16 years	–	–	–	0.734 (0.593 to 0.908)**
17–18 years	–	–	–	0.515 (0.384 to 0.687)***
19 years or older	–	–	–	0.432 (0.308 to 0.578)***
Occupational class				
Managerial and professional	–	–	–	Reference
Intermediate	–	–	–	1.390 (1.144 to 1.689)***
Routine and manual	–	–	–	1.614 (1.375 to 1.961)***

*p<0.05, **p<0.01, ***p<0.001.
†ORs (95% CI) for general cognitive ability are the odds of reporting being a current smoker for a 1 SD increase in general cognitive ability.
Age ^{2}, Age squared.

Health literacy, unlike already-established measures of socioeconomic status and perhaps more so than cognitive ability, is potentially modifiable.[31] Health literacy is thought to be the complex set of skills that are required to navigate all aspects of healthcare,[17 18] and include reading and numeracy skills, as well as health-related knowledge.[32] At least one component of health literacy—health knowledge—may be increased through educational programmes and interventions[32] and this in turn could lead to improved health outcomes.[33] Future research should examine whether cognitive ability and health literacy play a role in the success of smoking interventions, and should investigate whether interventions designed to increase smoking-specific health knowledge increase smoking cessation in individuals with limited health literacy.

This cross-sectional study was interested in examining the characteristics of smokers and, although a relationship between cognitive ability, health literacy and smoking cessation was identified, this study cannot determine the directionality of this association. It is possible that individuals who continue to smoke have lower cognitive ability and health literacy because smoking has damaging effects on both health literacy and cognitive ability. It is also possible that individuals who have lower cognitive ability and are less health literate are more likely to continue smoking because they do not have the cognitive capacity or the health-related knowledge and skills required to fully comprehend the adverse effects of continuing to smoke on health, or the knowledge and skills required to access and use smoking cessation services. For cognitive ability, evidence suggests that both of these pathways may be at least partially correct. Individuals with higher cognitive ability early in life are less likely to start smoking and more likely to quit,[10 12] and smoking may cause steeper cognitive change throughout life.[4–7] A similar relationship may exist between health literacy and smoking. Further longitudinal studies which include measures of cognitive ability and health literacy in early life are needed to understand the pathways between health literacy, cognitive ability and smoking.

The key strengths of this study include the large sample size and the fact that ELSA was designed to be representative of individuals aged over 50 residing in England.[19] One limitation is that smoking status was self-reported; however, self-reported smoking has been found to be in agreement with serum cotinine measurements.[34] The smoking measures used here do not take into account the amount smoked throughout life. These results reported here may underestimate the true effect sizes because lifetime smoking was not considered.

Another limitation of this study is that the cognitive ability and health literacy tests used here were brief.

Health literacy was assessed using a four-item test that was relatively insensitive to individual differences. That is, most individuals (67.3%) answered all questions correctly. Many, more detailed, health literacy assessments are available, such as the Test of Functional Health Literacy in Adults[35 36] which is thought to be the gold-standard measure of health literacy.[37] More detailed health literacy tests may be more sensitive to detecting associations between health literacy and health. However, the brief four-item measure of health literacy used in ELSA has been found to be associated with mortality[21] and participation in cancer screening,[22] suggesting it is sensitive enough to detect associations with health.

The measure of general cognitive ability created here was constructed using a small number of brief cognitive tests that did not include, for example, reasoning that is highly loaded on general cognitive ability.[38] A better general cognitive ability measure would have been possible had more domains of cognitive function been assessed, with more detailed tests. Given other studies which have suggested that some health literacy measures are essentially aspects of cognitive function,[30 39] and given also the limited cognitive test battery used in ELSA, it is possible that some of the independent contribution of the health literacy measure here is residual cognitive capability not picked up by the limited general cognitive ability component.

In this study of middle-aged and older adults, lower cognitive ability and poorer health literacy were associated with whether ever smokers continued to smoke, even after adjusting for education and occupational class. Further research is needed to identify possible pathways between health literacy, cognitive function and starting and quitting smoking.

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REFERENCES

1. Office for National Statistics. *Adult smoking habits in the UK*. England: Public Health England, 20162017. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2016. (accessed Jan 2018).
2. Allender S, Balakrishnan R, Scarborough P, *et al*. The burden of smoking-related ill health in the UK. *Tob Control* 2009;18:262–7.
3. Mons U, Schöttker B, Müller H, *et al*. History of lifetime smoking, smoking cessation and cognitive function in the elderly population. *Eur J Epidemiol* 2013;28:823–31.
4. Reitz C, Luchsinger J, Tang MX, *et al*. Effect of smoking and time on cognitive function in the elderly without dementia. *Neurology* 2005;65:870–5.
5. Richards M, Jarvis MJ, Thompson N, *et al*. Cigarette smoking and cognitive decline in midlife: evidence from a prospective birth cohort study. *Am J Public Health* 2003;93:994–8.
6. Anstey KJ, von Sanden C, Salim A, *et al*. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. *Am J Epidemiol* 2007;166:367–78.
7. Deary IJ, Pattie A, Taylor MD, *et al*. Smoking and cognitive change from age 11 to age 80. *J Neurol Neurosurg Psychiatry* 2003;74:1006–7.
8. Peters R, Poulter R, Warner J, *et al*. Smoking, dementia and cognitive decline in the elderly, a systematic review. *BMC Geriatr* 2008;8:36.
9. Corley J, Gow AJ, Starr JM, *et al*. Smoking, childhood IQ, and cognitive function in old age. *J Psychosom Res* 2012;73:132–8.
10. Batty GD, Deary IJ, Schoon I, *et al*. Mental ability across childhood in relation to risk factors for premature mortality in adult life: the 1970 British Cohort Study. *J Epidemiol Community Health* 2007;61:997–1003.
11. Hemmingsson T, Kriebel D, Melin B, *et al*. How does IQ affect onset of smoking and cessation of smoking-linking the Swedish 1969 conscription cohort to the Swedish survey of living conditions. *Psychosom Med* 2008;70:805–10.
12. Taylor MD, Hart CL, Davey Smith G, *et al*. Childhood mental ability and smoking cessation in adulthood: prospective observational study linking the Scottish Mental Survey 1932 and the midspan studies. *J Epidemiol Community Health* 2003;57:464–5.
13. Fernandez DM, Larson JL, Zikmund-Fisher BJ. Associations between health literacy and preventive health behaviors among older adults: findings from the health and retirement study. *BMC Public Health* 2016;16:596.
14. von Wagner C, Knight K, Steptoe A, *et al*. Functional health literacy and health-promoting behaviour in a national sample of British adults. *J Epidemiol Community Health* 2007;61:1086–90.
15. Geboers B, Reijneveld SA, Jansen CJ, *et al*. Health literacy is associated with health behaviors and social factors among older adults: Results from the lifelines cohort study. *J Health Commun* 2016;21:45–53.
16. Wolf MS, Gazmararian JA, Baker DW. Health literacy and health risk behaviors among older adults. *Am J Prev Med* 2007;32:19–24.
17. Institute of Medicine. *Health Literacy: A Prescription to End Confusion*. Washington DC: National Academies Press, 2004.
18. Baker DW. The meaning and the measure of health literacy. *J Gen Intern Med* 2006;21:878–83.
19. Steptoe A, Breeze E, Banks J, *et al*. Cohort profile: The english longitudinal study of ageing. *Int J Epidemiol* 2013;42:1640–8.
20. Thorn W. *International Adult Literacy and Basic Skills Surveys in the OECD Regresion. OECD Educatio Working Papers*. Paris: OECD Publishing, 2009.
21. Bostock S, Steptoe A. Association between low functional health literacy and mortality in older adults: longitudinal cohort study. *BMJ* 2012;344:e1602.
22. Kobayashi LC, Wardle J, von Wagner C. Limited health literacy is a barrier to colorectal cancer screening in england: Evidence from the english longitudinal study of ageing. *Prev Med* 2014;61:100–5.
23. Gale CR, Deary IJ, Wardle J, *et al*. Cognitive ability and personality as predictors of participation in a national colorectal cancer screening programme: The english longitudinal study of ageing. *J Epidemiol Community Health* 2015;69:530–5.
24. Salthouse TA. Selective review of cognitive aging. *J Int Neuropsychol Soc* 2010;16:754–60.
25. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol* 2009;60:173–96.
26. Rose D, Pevalin DJ, O'Reilly K. *The National Statistics Socio-economic Classification: origins, development and use*. Basingstoke, UK: Palgrave Macmillan, 2005.
27. Federman AD, Sano M, Wolf MS, *et al*. Health literacy and cognitive performance in older adults. *J Am Geriatr Soc* 2009;57:1475–80.
28. Kobayashi LC, Wardle J, Wolf MS, *et al*. Cognitive function and health literacy decline in a cohort of aging english adults. *J Gen Intern Med* 2015;30:958–64.

29. Murray C, Johnson W, Wolf MS, *et al*. The association between cognitive ability across the lifespan and health literacy in old age: The Lothian Birth Cohort 1936. *Intelligence* 2011;39:178–87.
30. Reeve CL, Basalik D. Is health literacy an example of construct proliferation? A conceptual and empirical evaluation of its redundancy with general cognitive ability. *Intelligence* 2014;44:93–102.
31. Nutbeam D. The evolving concept of health literacy. *Soc Sci Med* 2008;67:2072–8.
32. Chin J, Morrow DG, Stine-Morrow EA, *et al*. The process-knowledge model of health literacy: evidence from a componential analysis of two commonly used measures. *J Health Commun* 2011;16 Suppl 3(Suppl 3):222–41.
33. Rothman RL, DeWalt DA, Malone R, *et al*. Influence of patient literacy on the effectiveness of a primary care-based diabetes disease management program. *JAMA* 2004;292:1711–6.
34. Vartiainen E, Seppälä T, Lillsunde P, *et al*. Validation of self reported smoking by serum cotinine measurement in a community-based study. *J Epidemiol Community Health* 2002;56:167–70.
35. Parker RM, Baker DW, Williams MV, *et al*. The test of functional health literacy in adults: a new instrument for measuring patients' literacy skills. *J Gen Intern Med* 1995;10:537–41.
36. Baker DW, Williams MV, Parker RM, *et al*. Development of a brief test to measure functional health literacy. *Patient Educ Couns* 1999;38:33–42.
37. Mancuso JM. Assessment and measurement of health literacy: an integrative review of the literature. *Nurs Health Sci* 2009;11:77–89.
38. Salthouse T. Localizing age-related individual differences in a hierarchical structure. *Intelligence* 2004;32:541–61.
39. Mõttus R, Johnson W, Murray C, *et al*. Towards understanding the links between health literacy and physical health. *Health Psychol* 2014;33:164–73.

4.3. Conclusion

The results reported in Section 4.2 found that, when adjusting for age and sex only, limited health literacy and lower cognitive ability were associated with being more likely to report ever smoking. In participants who reported ever smoking, limited health literacy and lower cognitive ability were associated with being more like to report smoking nowadays (i.e., not quitting). These associations were reduced but remained significant when health literacy and cognitive ability were entered into the models concurrently. These findings indicate that health literacy and cognitive ability are separate, but related constructs, and both make unique contributions to smoking status. I note that, given the relatively brief nature of the cognitive ability measure used in this study, it is possible that health literacy was associated with smoking because of residual cognitive capability that is not being picked up by the brief measure of cognitive ability. As this is a possibility for a number of the studies reported in this thesis, this will be discussed in more detail in the general discussion (Chapter 8).

The association between health literacy and cognitive ability with reporting smoking nowadays remained significant even after adjustment for education and social class; however, the association between health literacy and cognitive ability with ever smoking was attenuated and non-significant when adjusting for these socioeconomic variables. This attenuation suggests that health literacy and cognitive ability do not have associations with ever smoking that are independent of education and social class.

The results reported in this chapter are consistent with Kobayashi et al. (2016b) who found that health literacy and cognitive ability have independent associations with participating in physical activity. Taken together the results reported in this chapter and the results reported in Kobayashi et al. (2016b) provide support that individuals with higher health literacy and cognitive ability are more likely to participate in health promoting behaviours; behaviours which may, in turn, reduce the risk of future morbidity and mortality. Chapter 5 will examine whether health literacy and cognitive ability are associated with reporting diabetes; a common chronic disease in older adulthood.

5. Health literacy, cognitive ability, and diabetes

5.1. Introduction

Chapter 4 investigated the association of health literacy and cognitive ability with smoking behaviour. Individuals with limited health literacy and lower cognitive ability were more likely to report having ever smoked, and, in those who reported ever smoking, were less likely to have quit. Certain health behaviours, including smoking, an unhealthy diet, and inactivity are known to increase the risk of common chronic diseases such as hypertension and diabetes (Forman, Stampfer, & Curhan, 2009; Huai et al., 2013; Hussain et al., 2007). Individuals with lower health literacy and cognitive ability might not have the cognitive and health-related skills to be able to take better care of themselves throughout life and are therefore at increased risk of developing chronic disease. The association between lower cognitive ability in early life and subsequent higher risk of developing chronic diseases is well established (Section 2.4.2). Less is known about whether health literacy is associated with chronic disease (Section 1.4.1); however, there is some cross-sectional evidence that those with lower health literacy are more likely self-report some chronic conditions including diabetes and cardiovascular conditions (Adams et al., 2009; Wolf, Davis, et al., 2005).

Using the ELSA sample, the present chapter will investigate whether health literacy and cognitive ability are associated with aspects of diabetes. In addition to examining the cross-sectional association between health literacy, cognitive ability, and diabetes status, the longitudinal nature of the ELSA cohort will be used to investigate whether health literacy and cognitive ability predict risk of developing diabetes in a sample of middle-aged and older adults over a 10 year follow-up period. This study has been submitted to *Diabetic Medicine* and the submitted paper is included in full in Section 5.2. The supplementary material for this paper is included in Appendix 1. A pre-print of this paper is available on MedRxiv (https://www.medrxiv.org/content/10.1101/19003756v1).

5.2. Health literacy, cognitive ability and self-reported diabetes in the English Longitudinal Study of Ageing (submitted)

Chloe Fawns-Ritchie[1,2] MSc, Jackie Price[3] MD, and Ian J Deary[1,2] PhD

Running title: Cognitive ability, health literacy and diabetes

[1]Department of Psychology, University of Edinburgh, Edinburgh, UK

[2]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK

[3]Usher Institute, University of Edinburgh, Edinburgh, UK

Corresponding author:

Chloe Fawns-Ritchie

Department of Psychology, University of Edinburgh

7 George Square

Edinburgh, EH8 9JZ

Scotland, UK

Telephone: +44 131 650 8317

c.fawns-ritchie@ed.ac.uk

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Abstract

Objective: To examine the association of health literacy and cognitive ability with risk of diabetes.

Research Design and Methods: Participants were 8,669 English Longitudinal Study of Ageing participants (mean age 66.7 years, SD 9.7) who completed health literacy and cognitive ability tests at wave 2 (2004-2005), and who answered a self-reported question on whether a doctor had ever diagnosed them with diabetes. Logistic regression was used to examine the cross-sectional associations of health literacy and cognitive ability with diabetes status. In those without diabetes at wave 2, Cox regression was used to test the associations of health literacy and cognitive ability with risk of diabetes over a median of 9.5 years follow-up (n=6,961).

Results: Adequate (compared to limited) health literacy (OR 0.72, 95% CI 0.61-0.84) and higher cognitive ability (OR per 1 SD 0.73, CI 0.67-0.80) were both associated with lower odds of self-reported diabetes. Adequate health literacy (HR 0.64; CI 0.53-0.77) and higher cognitive ability (HR 0.77, CI 0.69-0.85) were also associated with lower risk of self-reporting diabetes during follow-up. When both health literacy and cognitive ability were added to the same model, these associations were slightly attenuated. Additional adjustment for health behaviours, education and social class attenuated associations further, and neither health literacy nor cognitive ability were significantly associated with diabetes.

Conclusions: Adequate health literacy and better cognitive ability were associated with reduced risk of diabetes. These associations were independent of each other, but not of other health- and socioeconomic-related variables.

5.2.1. Introduction

Diabetes is a common chronic condition in older adulthood and is associated with substantial morbidity and mortality (Diabetes UK, 2014). Type 2 diabetes, the most common type of diabetes, is at least partly preventable (Hussain et al., 2007). Understanding the characteristics of those most at risk of developing diabetes is important to appropriately target diabetes education and interventions. Known risk factors for developing diabetes include older age, deprivation, and obesity (Diabetes UK, 2014; Hussain et al., 2007).

Lower cognitive ability may be a risk factor for diabetes. Whereas one study (Batty, Deary, & Macintyre, 2007) found that childhood cognitive ability did not predict diabetes in midlife, others have found that lower cognitive ability in early life was associated with higher risk of diabetes in adulthood (Mõttus et al., 2013; Twig et al., 2014). In a sample of Scottish older adults who had their cognitive ability tested in childhood (Mõttus et al., 2013), a 1 SD advantage in cognitive ability was associated with 26% lower odds of reporting diabetes in older age. Individuals with higher cognitive ability might have the cognitive skills required to self-manage their health, take better care of themselves throughout life, and thus reduce the risk of developing diabetes (Gottfredson, 2004; Mõttus et al., 2013).

Health literacy, of which cognitive ability is thought to be a prerequisite (Paasche-Orlow & Wolf, 2007), might also play a role in diabetes risk. Health literacy is the “capacity to obtain, process and understand basic health information and services needed to make basic health decisions” (Nielsen-Bohlman et al., 2004). In cross-sectional studies, rates of diabetes are higher in those with low health literacy (Adams et al., 2009; Wolf, Gazmararian, et al., 2005). In one study, participants with inadequate health literacy were 48% more likely to report having diabetes when compared to participants with adequate health literacy, even after adjusting for sociodemographic and health variables (Wolf, Gazmararian, et al., 2005). Individuals with lower health literacy might not have the health-related skills required to obtain, understand and follow health advice, such as eating well and exercising, which might reduce the risk of diabetes (Nielsen-Bohlman et al., 2004).

In individuals with diabetes, higher health literacy has consistently been associated with greater diabetes knowledge (Al Sayah et al., 2013; Caruso et al., 2018; Marciano et al., 2019). A very small association between higher health literacy and lower HbA1c levels in patients with diabetes has also been reported in a meta-analysis based on 26 studies (r=-0.048, p=0.027; Marciano et al., 2019). Whereas studies have investigated the association between health literacy and disease management in people with diabetes, little is known about whether health literacy is associated with risk of developing diabetes.

Health literacy and cognitive ability test scores are positively correlated (J. S. Bennett et al., 2012; Murray et al., 2011). In one study, rank-order correlations between a measure of general cognitive ability and three health literacy tests ranged from 0.37 to 0.50 (Murray et al., 2011). These correlations with cognitive ability tended to be higher than the correlations between the three health literacy tests themselves (*rho* = 0.28 to 0.46; Murray et al., 2011) . Researchers have sought to determine the role of cognitive ability in the association between health literacy and a range of health outcomes. Most (but not all; Lamar et al., 2019) studies have found that cognitive ability partly or entirely attenuates the association between health literacy and health (Baker et al., 2008; Bostock & Steptoe, 2012; Fawns-Ritchie, Starr, & Deary, 2018a; Mõttus et al., 2014). It is possible that any association between health literacy and diabetes may be attenuated when also measuring cognitive ability.

The aim of the current study was to better understand the associations of health literacy and cognitive ability with risk of diabetes. Using participants from the English Longitudinal Study of Ageing (ELSA), a cohort study designed to be representative of adults aged over 50 years living in England (Steptoe, Breeze, Banks, & Nazroo, 2013), the present study investigated whether health literacy and cognitive ability were independently associated with self-reported diabetes status. First, the cross-sectional associations between health literacy, cognitive ability, and self-reported diabetes were investigated. Second, individuals without diabetes at baseline were followed-up for up to 10 years to determine whether health literacy and cognitive ability were independently associated with subsequent risk of diabetes in mid-to-later life.

5.2.2. Methods

5.2.2.1. Participants

This study used data from core members of the ELSA study, a prospective cohort study of community-dwelling adults residing in England. The wave 1 (2002-2003) sample consisted of 11,391 participants who had previously participated in the Health Survey for England and who were living in a private household (Steptoe et al., 2013). ELSA participants have been followed up every two years.

The main interview consisted of participants answering questions on health, lifestyle and economic circumstances via a Computer Assisted Personal Interview (CAPI). Participants were asked to complete a self-completion questionnaire which assessed topics including diet and alcohol consumption. A nurse visit was carried out every second wave to assess physical measurements including height and weight, and blood and saliva samples were taken to measure biomarkers of disease. A detailed description of the sample design and the data collected in ELSA is reported elsewhere (Steptoe et al., 2013). The present study used data from waves 2 to 7. For the present study, baseline was considered to be Wave 2 (2004-2005; n=8,726), which was when the health literacy assessment was introduced.

5.2.2.2. Measures

Diabetes

Two measures of diabetes, collected during the CAPI, were used as outcome variables in this study.

Baseline diabetes status: Individuals who answered “yes” to “Has a doctor ever told you that you have diabetes?” at wave 2 were categorised as having diabetes. This question did not differentiate which type of diabetes the participant was diagnosed with. A previous study reported a high rate of agreement between self-reported diabetes and fasting blood glucose in a subsample of ELSA participants with data on both self-reported diabetes status and fasting blood glucose levels (Pierce, Zaninotto, Steel, & Mindell, 2009).

Incident diabetes: For incident diabetes, the analysis was restricted to participants who did not self-report diabetes at wave 2 and who had at least one wave of follow-up between waves 3 and 7. Participants who did not self-report diabetes at wave 2 and who subsequently answered “yes” to “Has a doctor ever told you that you have diabetes?” were categorised as having incident diabetes. As all participants were aged over 50 years at diagnosis, these cases are probably cases of type 2 diabetes.

Date of diabetes diagnosis: Individuals who self-reported diabetes were asked which month and year they were diagnosed. Date of diabetes diagnosis was used to calculate the time between wave 2 assessment and diabetes diagnosis.

Health literacy

A brief 4-item health literacy test was administered during the CAPI at wave 2. This test assessed health-related reading comprehension skills which are thought to be required to successfully understand written health materials commonly encountered in healthcare. Participants were presented with a piece of paper containing a label for a packet of over-the-counter medication. Participants were asked four questions about the information on this label (e.g., "what is the maximum number of days you may take this medicine?"). The score was the number of correctly answered questions. As has been done in other studies (Gale, Deary, Wardle, Zaninotto, & Batty, 2015; Kobayashi et al., 2014), performance was categorised as adequate (4/4 correct) or limited (<4 correct).

Cognitive ability

Four tests administered during the wave 2 CAPI were used to create a measure of general cognitive ability. Immediate and delayed word recall were used to assess verbal declarative memory. In the immediate recall test, participants were read a list of 10 words and were asked to immediately recall as many of the words as possible. The score was the number of words recalled immediately. After a short delay, in which the words were not repeated, participants were asked to remember the 10 words again. The score was the number of words recalled after a delay. Executive function was assessed with a verbal fluency test. Participants were instructed to name as many animals as possible. The score was the number of animals named within the 60 second time limit. Letter cancellation was used to assess processing speed. Participants were presented with a piece of paper containing letters of the alphabet arranged in rows and columns. The task was to scan the piece of paper and score out all Ps and Ws. The score was the combined number of Ps and Ws scored out in 60 seconds.

Scores of 0 on animal fluency (n=48) and letter cancellation (n=3) were removed as this suggests participants did not complete the task or did not understand the task. Scores of 50 or more on animal fluency (n=4), and 60 or more on the letter cancellation (n=3) were removed as these scores were questionably high given the test time limits. Scores on the four cognitive ability tests were then entered into a principal component analysis (PCA). Only the first component had an eigenvalue >1, and the scree plot also indicated one component. Scores from the first principal component were saved and used as a measure of cognitive ability. The first component accounted for 57% of the variance in the scores on the four cognitive tests. The loadings were: Immediate word recall=0.83, delayed word recall=0.85, animal fluency=0.72, and letter cancellation=0.58. The resultant cognitive ability score was a z-score (mean 0.00, SD 1.00).

Covariates

Age (in years), sex, BMI, health behaviours, number of cardiovascular comorbidities, and measures of socioeconomic status were used as covariates. Unless otherwise stated, all covariates were self-reported at the wave 2 CAPI. Participants aged over 90 years had their age set to 90 as there were so few of them. Participants were asked whether they smoked cigarettes nowadays and were categorised as current smokers or non-smokers. Participants were asked how often they took part in moderate and vigorous physical activity (more than once a week, once a week, one to three times a month, and hardly ever/never). Physical activity levels were categorised as vigorous activity at least once per week, moderate activity at least once per week, and physically inactive. Participants were asked about their frequency of alcohol consumption in the past 12 months in the self-completion questionnaire. This was categorised as never, rarely, at least once a month, at least once a week, and daily/almost daily. Height and weight, measured during the wave

2 nurse interview, were used to calculate BMI (kg/m^2). Cardiovascular comorbidities were assessed by counting the number of self-reported cardiovascular conditions from hypertension, angina, heart attack, heart murmur, abnormal heart rhythm, stroke, and high cholesterol. Age that participants left full-time education was categorised as: age 14 or under, 15-16 years, 17-18 years, and age 19 or older. Social class was categorised using the National Statistics Socioeconomic Classification 3 categories (Rose, Pevalin, & O'Reilly, 2005): managerial and professional, intermediate, and routine and manual.

5.2.2.3. Analysis

Independent t-tests were used to compare those with and without diabetes at wave 2 and those who did and did not develop diabetes at follow-up on normally-distributed continuous variables. Mann-Whitney U tests were used for non-normal continuous variables, and Chi-squared tests were used for categorical variables. Spearman rank-order correlations were calculated between all predictor variables and co-variables.

Binary logistic regression was used to test the cross-sectional association of health literacy and cognitive ability with wave 2 diabetes status. Cox regression was used to investigate whether health literacy and cognitive ability test scores at wave 2 predicted risk of developing diabetes between waves 2 and 7. In the Cox regression analysis, time-to-event was taken as the difference, in days, between date of wave 2 CAPI and date of diabetes diagnosis for those who self-reported diabetes. For all other participants, time-to-event was the difference between date of wave 2 CAPI interview and the date of last CAPI interview. Month and year, but not day, were recorded for date of CAPI interview and date of diabetes diagnosis. To create a date variable (yyyy.mm.dd), the day was set to the middle of the month.

For the logistic regression and Cox regression, 6 models were run. Age and sex were entered into all models. Health literacy and cognitive ability were entered individually in models 1 and 2, respectively. Both health literacy and cognitive ability were added in Model 3 to determine whether the size of the health literacy-diabetes and cognitive ability-diabetes associations changed when concurrently entering both these variables in the model. To assess whether BMI and health behaviours accounted for these associations, BMI, smoking status, alcohol consumption, and physical activity were added in Model 4. Diabetes is a risk factor for cardiovascular disease (Sarwar et al., 2010). Associations between poorer cognitive ability and cardiovascular disease are also well established (Hart et al., 2004; Rostamian et al., 2014). It is possible that any association between health literacy and cognitive ability with diabetes may be because of these associations with cardiovascular disease. To determine whether any association between health literacy and cognitive ability with diabetes was attenuated when adjusting for cardiovascular disease, number of cardiovascular comorbidities was additionally added in Model 5. Age of leaving full-time education and occupational social class were added in Model 6 to determine whether the association between health literacy, cognitive ability and diabetes was attenuated when accounting for these commonly-used indicators of socioeconomic status.

This study was interested in the associations of health literacy and cognitive ability with self-reported diabetes and the independence of these associations with respect to other health and socioeconomic-related variables. In the main text we report the ORs (95% CIs) and the HRs (95% CIs) for health literacy and cognitive ability only. The estimates for all covariates entered into the models are reported in the Supplementary materials.

5.2.3. Results

Of the 8,726 ELSA participants who completed the wave 2 assessment, 3 participants were removed who answered “don’t know” to whether a doctor had diagnosed them with diabetes. A further 54 were removed because these individuals selected that they had “diabetes or high blood sugar” from a Showcard listing cardiovascular conditions, but, when asked whether a doctor had ever told them they had diabetes, they answered “no”. Thus, the analytic sample consisted of 8,669 participants. Participant characteristics are reported in Table 1.

5.2.3.1. Baseline diabetes status

At baseline 708 (8.2%) of participants self-reported a doctor diagnosis of diabetes. Compared to those without diabetes, those with diabetes were more likely to have limited health literacy (42.2% versus 32.3%; $p<.001$) and have lower cognitive ability scores (diabetes mean -0.36, SD 0.97; no diabetes mean 0.03, SD 1.00; Cohen’s *d* 0.40; $p<.001$). Compared to participants without diabetes, participants with diabetes at wave 2 were older, more likely to be male, tended to leave full-time education at a younger age, be from a less professional social class, have a higher BMI, consume less alcohol, be inactive, and self-report more cardiovascular comorbidities. Rank-order correlations between the predictor variables and co-variables are reported in Table 2. Adequate health literacy was moderately correlated with higher scores on cognitive ability (*rho*=0.31, p<.001).

Table 5.1. Participant characteristics by diabetes status in the English Longitudinal Study of Ageing (ELSA)

	Baseline diabetes status reported at wave 2 of ELSA				Incident diabetes reported at follow-up*			
	n	No diabetes (n = 7961)	Diabetes (n = 708)	p	n	No diabetes (n = 6455)	Diabetes (n = 506)	p
Age	8669	66.46 (9.70)	69.38 (9.16)	< .001	6961	66.02 (9.53)	65.51 (8.59)	< .001
Sex	8669			< .001	6961			< .001
Male		3522 (44.2%)	379 (53.5%)			2791 (43.2%)	262 (51.8%)	
Female		4439 (55.8%)	329 (46.5%)			3664 (56.8%)	244 (48.2%)	
Age left full-time education	8468			< .001	6809			< .001
<14 years		1641 (21.1%)	210 (30.6%)			1222 (19.3%)	107 (21.8%)	
15-16 years		4085 (52.5%)	349 (50.8%)			3283 (52.0%)	302 (61.6%)	
17-18 years		1009 (13.0%)	55 (8.0%)			870 (13.8%)	45 (9.2%)	
19+ years		1046 (13.4%)	73 (10.6%)			944 (14.9%)	36 (7.3%)	
Social class	8508			< .001	6846			< .001
Managerial and professional		2444 (31.2%)	194 (28.4%)			2067 (32.6%)	133 (26.7%)	
Intermediate		1979 (25.3%)	131 (19.2%)			1662 (26.2%)	104 (20.9%)	
Routine and manual		3403 (43.5%)	357 (52.3%)			2619 (41.3%)	261 (52.4%)	
Health literacy	8293			< .001	6736			< .001
Adequate		5172 (67.7%)	376 (57.8%)			4351 (69.7%)	300 (61.2%)	
Limited		2471 (32.3%)	274 (42.2%)			1895 (30.3%)	190 (38.8%)	
Cognitive ability	8335	0.03 (1.00)	-0.36 (0.97)	< .001	6746	0.10 (0.98)	-0.04 (0.89)	< .001
BMI	7179	27.71 (4.79)	30.45 (5.37)	< .001	5997	27.46 (4.64)	31.21 (5.28)	< .001
Current smoker	8622			0.377	6929			< .001
Yes		1216 (15.4%)	99 (14.1%)			934 (14.5%)	105 (20.8%)	
No		6704 (84.6%)	603 (85.9%)			5490 (85.5%)	400 (79.2%)	

Alcohol	7577			< .001	6239			< .001
Never		723 (10.3%)	112 (19.3%)			565 (9.7%)	49 (11.2%)	
Rarely		1076 (15.4%)	124 (21.3%)			863 (14.9%)	90 (20.6%)	
At least once a month		827 (11.8%)	85 (14.6%)			669 (11.5%)	70 (16.1%)	
At least once a week		2662 (38.1%)	171 (29.4%)			2255 (38.9%)	149 (34.2%)	
Daily/almost daily		1708 (24.4%)	89 (15.3%)			1451 (25.0%)	78 (17.9%)	
Physical activity	8665			< .001	6958			< .001
Vigorous activity		2236 (28.1%)	108 (15.2%)			1938 (30.0%)	116 (22.9%)	
Moderate activity		3888 (48.9%)	305 (43.1%)			3194 (49.5%)	233 (46.0%)	
Inactive		1833 (23.0%)	295 (41.7%)			1320 (20.5%)	157 (31.0%)	
Number of cardiovascular comorbidities	8669	0.67 (0.91)	1.28 (1.13)	< .001	6961	0.64 (0.88)	0.89 (1.04)	< .001

Scores are mean (SD) for continuous variables and count (percentage) for categorical variables. BMI, body mass index.
*Incident diabetes reported at follow-up comparisons are based on a subsample of participants who did not self-report a diagnosis of diabetes at wave 2 and with at least one wave of follow-up.

Table 5.2. Spearman rank-order correlations between covariates (n=6,463 to 8,660)

	Age	Sex	Education	Social class	Health literacy	Cognitive ability	BMI	Smoking	Alcohol	Physical activity	CV comorbid
Age	-										
Sex	-0.03**	-									
Education	-0.41***	0.02	-								
Social class	0.08***	-0.09***	-0.41***	-							
Health literacy	-0.16***	0.01	0.23***	-0.18***	-						
Cognitive ability	-0.47***	-0.09***	0.39***	-0.27***	0.31***	-					
BMI	-0.07***	0.02	-0.06***	0.08***	-0.04**	-0.01	-				
Smoking	-0.13***	0.01	-0.05***	0.12***	-0.04***	-0.02	-0.09***	-			
Alcohol	-0.11***	0.21***	0.22***	-0.20***	0.09***	0.16***	-0.11***	-0.04***	-		
Physical activity	-0.26***	0.10***	0.23***	-0.15***	0.14***	0.26***	-0.11***	-0.09***	0.18***	-	
CV comorbid	0.18***	0.00	-0.11***	0.05***	-0.06***	-0.11***	0.14***	-0.03*	-0.08***	-0.14***	-

$^*p < .05$, $^{**}p < .01$, $^{***}p < .001$

BMI, body mass index; CV comorbid, number of cardiovascular comorbidities.

Sex is coded 0 for female, 1 for male; Education is age of leaving full-time education and is coded 1 for age 14 years or less, 2 for age 15-16 years, 3 for age 17-18 years, and 4 for 19 years or older; Social class is coded 1 for managerial and professional, 2 for intermediate, and 3 for routine and manual; Health literacy is coded 0 for limited and 1 for adequate; Smoking is coded 0 for current non-smoker and 1 for current smoker; Alcohol is the frequency of alcohol consumed in the last 12 months and is coded 0 for never, 1 for rarely, 2 for at least once a month, 3 for at least once a week, 4 for daily/almost daily; Physical activity is coded 0 for inactive, 1 for moderate activity at least once per week, 2 for vigorous activity at least once per week; CV comorbid is the number of cardiovascular comorbidities self-reported from hypertension, angina, heart attack, heart failure, heart murmur, abnormal heart rhythm, stroke, and high cholesterol.

The ORs and 95% CIs for the associations of health literacy and cognitive ability with self-reported diabetes at wave 2 are reported in Table 3 (full results are reported in Supplementary Table S1). A Box-Tidwell test found that the assumption of linearity of the logit was violated. Therefore an age-squared term was included in all models, and a squared term for number of cardiovascular comorbidities was included in models 5 and 6. Individuals with adequate health literacy were 28% less likely to self-report diabetes at wave 2 (Model 1; OR 0.72, 95% CI 0.61-0.84). A 1 SD higher cognitive ability was associated with a 27% lower odds of self-reporting diabetes (Model 2; OR 0.73, 95% CI 0.67-0.80). The association between health literacy and diabetes was attenuated by 36% (OR 0.82, 95% CI 0.69-0.98) and the association between cognitive ability and diabetes was attenuated by 19% (OR 0.78, 95% CI 0.70-0.86) when entering both health literacy and cognitive ability in Model 3. Both remained significantly associated with diabetes. The association between health literacy and cognitive ability with diabetes was attenuated and no longer significant when additionally adjusting for BMI and health behaviours in Model 4. Health literacy and cognitive ability remained non-significant after adjustment for cardiovascular comorbidities (Model 5), and for education and social class (Model 6).

In the fully-adjusted model (Model 6; Supplementary Table S1) older age, being male, having a higher BMI, and reporting a higher number of cardiovascular comorbidities were associated with higher odds of having diabetes at wave 2. The association between number of cardiovascular comorbidities and diabetes became less strong as the number of comorbidities increased. Those who reported drinking alcohol at least once per month, rarely, or who never drank alcohol in the last 12 months were more likely to self-report diabetes when compared to those who reported drinking daily/almost daily. Compared to those who reported being physically inactive, those who took part in moderate or vigorous physical activity at least once per week were less likely to self-report diabetes.

5.2.3.2. Risk of incident diabetes

Of the 7,961 participants who did not self-report diabetes at wave 2, 6,961 participants had at least one wave of follow-up between waves 3 and 7. They form the analytic sample for the association between health literacy, cognitive ability and risk of incident diabetes. A total of 506 (7.3%) participants reported a new diagnosis of diabetes between wave 3 and wave 7, whereas 6,455 (92.7%) participants did not. Median time to follow-up was 9.5 years. Mean time to censor for those with diabetes, who were censored at date of diabetes diagnosis, was 4.7 years (SD 3.1). Mean time to censor for those not diagnosed with diabetes, who were censored at date of last CAPI interview, was 7.8 years (SD 2.9). Characteristics for participants with and without diabetes at follow-up are shown in Table 1. Compared to participants who did not have incident diabetes, those who did were more likely to have limited health literacy (38.8% versus 30.3%, $p<.001$) and had lower cognitive ability scores (diabetes mean -0.04, SD 0.89; no diabetes mean 0.10, SD 0.98, Cohen's d 0.15, $p<.001$) at wave 2. Compared to those who did not develop diabetes, participants who developed diabetes were older, more likely to be male, have left full-time education at a younger age, be from a less professional social class, smoke, consume less alcohol, be inactive, and to report more cardiovascular comorbidities at wave 2.

Table 5.3. Odds ratios (95% CI) from logistic regression models of the association between health literacy and cognitive ability with whether participants self-reported a diagnosis of diabetes at wave 2 of the English Longitudinal Study of Ageing

	Model 1: Health literacy	Model 2: Cognitive ability	Model 3: Health literacy and cognitive ability	Model 4: + BMI and health behaviours	Model 5: + CV comorbidities	Model 6: + education and social class
Adequate health literacy	0.72*** (0.61 to 0.84)	-	0.82* (0.69 to 0.98)	0.97 (0.78 to 1.21)	1.00 (0.81 to 1.26)	0.98 (0.78 to 1.23)
Cognitive ability	-	0.73*** (0.67 to 0.80)	0.78*** (0.70 to 0.86)	0.90 (0.80 to 1.02)	0.90 (0.79 to 1.02)	0.88 (0.77 to 1.00)

*p < .05, **p < .01, ***p < .001

BMI, body mass index; CV, cardiovascular.

Models 1 (n=8,293), 2 (n=8,335), and 3 (n=8,185) adjusted for age, age-squared and sex. Model 4 (n=6,302) adjusted for age, age-squared, sex, body mass index, frequency of alcohol consumption in the past 12 months, and physical activity. Model 5 (n=6,302) adjusted for Model 4 covariates, number of cardiovascular comorbidities reported, and a squared term for number of cardiovascular comorbidities reported. Model 6 (n=6,086) adjusted for Model 5 covariates, age left full-time education, and occupational social class.

The HRs and 95% CIs for the association between health literacy, cognitive ability and risk of diabetes are reported in Table 4 (full results reported in Supplementary Table S2). Adequate health literacy at wave 2 was associated with a 36% lower risk of developing diabetes (Model 1; HR 0.64, 95% CI 0.53-0.77). A 1 SD higher cognitive ability score at wave 2 was associated with a 23% lower risk of developing diabetes (Model 2; HR 0.77, 95% CI 0.69-0.85). The association between health literacy and risk of diabetes was attenuated by 22% after adjustment for cognitive ability (Model 3; HR 0.72, 95% CI 0.59-0.87), and the association between cognitive ability and risk of diabetes was attenuated by 9% after adjusting for health literacy (HR 0.79, 95% CI 0.71-0.88). Both health literacy and cognitive ability remained significant predictors of diabetes risk. BMI and health behaviours were additionally added to the model in Model 4. The associations of health literacy (HR 0.79, 95% CI 0.64-0.99) and cognitive ability (HR 0.85, 95% CI 0.74-0.96) with diabetes risk were further attenuated but remained statistically significant. When additionally adjusting for number of cardiovascular comorbidities, the association between health literacy and cognitive ability with risk of diabetes remained almost unchanged (Model 5). After adjustment for age at leaving full-time education and social class, the associations of health literacy and cognitive ability with risk of diabetes were further attenuated and non-significant.

In the fully-adjusted model (Model 6; Supplementary Table S2) male participants, those with a higher BMI, current smokers, and those who reported consuming alcohol rarely (compared to those who reported consuming alcohol daily/almost daily) at wave 2 had an increased risk of diabetes. Participants who reported leaving education at age 19 years or older had a lower risk of diabetes when compared to those who left education at age 14 years or younger.

Table 5.4. Hazard ratios (95% CI) from Cox regression models of the association between health literacy and cognitive ability with risk of incident diabetes

	Model 1: Health literacy	Model 2: Cognitive ability	Model 3: Health literacy and cognitive ability	Model 4: + BMI and health behaviours	Model 5: + CV comorbidities	Model 6: + education and social class
Adequate health literacy	0.64*** (0.53 to 0.77)	-	0.72*** (0.59 to 0.87)	0.79* (0.64 to 0.99)	0.80* (0.64 to 0.99)	0.85 (0.68 to 1.06)
Cognitive ability	-	0.77*** (0.69 to 0.85)	0.79*** (0.71 to 0.88)	0.85* (0.74 to 0.96)	0.85* 0.74 to 0.96)	0.88 0.77 to 1.01)

*$p < .05$, **$p < .01$, ***$p < .001$

BMI, body mass index, CV, cardiovascular.

Models 1 (n=6,736; 490 diabetes events), 2 (n=6,746; 491 diabetes events), and 3 (n=6,654; 484 diabetes events) adjusted for age, and sex. Model 4 (n=5,357; 377 diabetes events) adjusted for age, sex, body mass index, frequency of alcohol consumption in the past 12 months, and physical activity. Model 5 (n=5,357; 377 diabetes events) adjusted for Model 4 covariates, and number of cardiovascular comorbidities reported. Model 6 (n=5,186; 360 diabetes events) adjusted for Model 5 covariates, age left full-time education, and occupational social class.

5.2.3.3. Sensitivity analysis

There were some missing data. For the cross-sectional analyses, 70% of participants had complete data. For the longitudinal analyses, 75% of participants had complete data. All models were re-run using only participants with complete data on all variables entered into the models. These results are reported in Supplementary Tables S3 and S4. The pattern of associations were generally similar; however, the sizes of the associations tended to be slightly weaker compared to the full sample. For the cross-sectional analysis, health literacy was no longer significantly associated with diabetes status in Model 3 when adjusting for health literacy and cognitive ability (Supplementary Table S3). For the longitudinal analysis, when adjusting for BMI and health behaviours (Model 4; Supplementary Table S4), health literacy was no longer associated with risk of diabetes.

5.2.4. Discussion

Using a sample of middle-aged and older adults living in England, the present study found that adequate health literacy and better cognitive ability were associated with lower odds of reporting diabetes. The associations of health literacy and cognitive ability with diabetes status were attenuated and non-significant when additionally adjusting for BMI and health behaviours. Adequate health literacy and better cognitive ability, measured at wave 2, were associated with reduced risk of developing diabetes during a median of 9.5 years follow-up. Health literacy and cognitive ability predicted risk of diabetes both when examined individually and when examined concurrently. These associations were attenuated, though remained significant, when adjusting for BMI and health behaviours. When additionally adjusting for education and social class, the associations between health literacy and cognitive ability with diabetes risk were no longer significant. The results of the current study suggest that health literacy and cognitive ability have overlapping and unique associations with risk of diabetes. However, the relationship of health literacy and cognitive ability with diabetes is attenuated by health behaviours and education.

Previous cross-sectional studies have found that individuals with lower health literacy are more likely to report having diabetes (Adams et al., 2009; Wolf, Gazmararian, et al., 2005) and longitudinal studies have found that that lower cognitive ability earlier in life is associated with an increased risk of diabetes (Mõttus et al., 2013; Twig et al., 2014). The present study is the first longitudinal study to examine whether health literacy is associated with risk of developing diabetes, and the first to examine whether cognitive ability and health literacy have independent associations with diabetes.

The association between health literacy and cognitive ability can at times be so strong that some have suggested that health literacy and cognitive ability are not unique constructs and, instead, that health literacy variance is mostly overlapping with cognitive ability (Mõttus et al., 2014; Reeve & Basalik, 2014). If this were true, one would expect the association between health literacy and diabetes to be fully attenuated when adjusting for cognitive ability. This is not what was found in the current study. The association between health literacy and diabetes was only moderately attenuated (by 36% for baseline diabetes status and by 22% for diabetes risk) when adjusting for cognitive ability; moreover, both remained significant predictors of diabetes. The results suggest that only some of the association of health literacy with diabetes status and with diabetes risk was accounted for by cognitive ability.

However, there is a necessary caveat to that possible conclusion. The cognitive ability measure created in the current study used four brief cognitive ability tests that assessed memory, executive function and processing speed, and did not include other important domains of cognitive function, such as reasoning, that are known to load highly on general cognitive ability (Salthouse, 2004). It is possible that some of the unique contribution of health literacy might be residual cognitive capability that was not picked up by the relatively brief measures of cognitive ability used (Fawns-Ritchie, Starr, & Deary, 2018b). It is also not appropriate to compare the strength of the health literacy-diabetes and cognitive ability-diabetes associations due to the differences in measurement. Cognitive ability was assessed using a continuous measure created using scores on multiple cognitive ability tests, whereas health literacy scores were dichotomised into two groups (adequate and limited health literacy) based on performance on a brief, four-item test.

We found that the associations between health literacy and cognitive ability with cross-sectional diabetes status and with risk of diabetes were fully and partly attenuated, respectively, when adjusting for BMI and health behaviours. Better cognitive ability has been associated with health promoting behaviours such as following a healthy diet and taking part in regular exercise (Batty, Deary, & Macintyre, 2007; Batty, Deary, et al., 2007a, 2007b; Wraw et al., 2018). Whereas some studies have found associations between better health literacy and taking part in health promoting behaviours (von Wagner et al., 2007), others have not (Wolf et al., 2007). Individuals with higher health literacy and cognitive ability might tend to be better equipped with the skills and abilities needed to take better care of themselves (Deary, Weiss, et al., 2010; Gottfredson, 2004) and to follow health advise including eating well and exercising, which, in turn, reduces the risk of developing diabetes (Hussain et al., 2007).

Education attenuated and nullified the association between health literacy and cognitive ability with risk of diabetes. The association between better health literacy and cognitive ability with higher levels of education are well established (Deary, Strand, Smith, & Fernandes, 2007; Nielsen-Bohlman et al., 2004). Education may lead to better cognitive ability and health literacy, which in turn may lead to better health-related skills and lower rates of diabetes (Mõttus et al., 2014). Higher early life cognitive ability has been found to predict later educational attainment (Deary, Strand, et al., 2007). Therefore, an alternative, but not mutually exclusive, explanation could be that higher cognitive ability may equip an individual with the skills needed to obtain higher educational qualifications. Higher educational attainment, in turn, may lead to better health (and lower risk of diabetes) by, for example, increasing health-related knowledge and decision-making skills (Mõttus et al., 2014). It is possible that including education in the models could be over-adjusting.

This study has a number of strengths and limitations. A key strength is that it examined the association of health literacy, cognitive ability and risk of incident diabetes longitudinally. Another strength is the relatively large sample size. One limitation is that only a subsample of participants had complete data. Those with missing data may be those with the lowest health literacy and cognitive ability scores. ELSA may also suffer from selective attrition such that those with increased risk of diabetes may be less likely to return for follow-up. Therefore, the results reported here may not generalise to those with the lowest health literacy and/or cognitive ability, and those with the highest risk of diabetes. Diabetes status was self-reported. However, there is a relatively high rate of agreement between self-reported diabetes and fasting blood glucose in ELSA (Pierce et al., 2009). Only 1.7% of ELSA participants had undiagnosed diabetes, which is much lower than has been found in other cohort studies (Pierce et al., 2009). The health literacy test used in the current study was a brief, four-item test which had limited variance (67% of participants scored the highest score). Although brief, this test was sensitive enough to predict diabetes risk in the current study, and it has previously been found to predict mortality (Bostock & Steptoe, 2012).

This study found that both adequate health literacy and higher cognitive ability were independently associated with lower odds of self-reporting diabetes and with reduced risk of developing diabetes during a median of 9.5 years follow-up. These associations were attenuated by health behaviours and education. Individuals with poor health literacy and/or cognitive ability might tend to lack the health-related and cognitive skills and knowledge required to look after their health throughout life, which in turn, may increase the risk of diabetes. Future studies should investigate whether interventions designed to improve the knowledge and skills required to better self-manage health reduce the risk of developing diabetes in individuals with low health literacy and cognitive ability.

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Author Contributions. CF-R discussed and planned the study, performed the statistical analysis, interpreted the data, and drafted the manuscript. JP discussed and planned the study, interpreted the data, and contributed to the manuscript. IJD discussed and planned the study, interpreted the data, and contributed to the manuscript. CF-R is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

5.3. Conclusion

This chapter investigated the role of health literacy and cognitive ability with cross-sectional diabetes status and with risk of developing diabetes during a median of 9.5 years of follow-up. This study found that adequate health literacy and better cognitive ability, when examined individually, were associated with lower odds of self-reporting diabetes, and with lower risk of developing diabetes during follow-up. When health literacy and cognitive ability were entered concurrently, the size of the associations between health literacy and diabetes, and cognitive ability and diabetes, were reduced, but both health literacy and cognitive ability remained significantly associated with diabetes status and risk of developing diabetes during follow-up. These results suggest that the contents of the health literacy and cognitive ability tests partly overlap, but that both health literacy and cognitive ability have independent associations with risk of diabetes. An alternative possibility is that some of the unique contribution of health literacy might be residual cognitive ability that is not being captured by the brief measure of cognitive ability used in this study. This will be discussed in detail in Chapter 8. These associations were attenuated by health behaviours and socioeconomic variables, and, in the fully-adjusted model, neither health literacy nor cognitive ability were associated with diabetes status.

Taken together, this chapter and Chapter 4 provide support that health literacy and cognitive ability are related, but unique constructs, given the tests that were used to assess cognitive ability and health literacy. Chapter 4 found that health literacy and cognitive ability have independent associations with ever smoking and continuing to smoke; behaviours known to increase the risk of morbidity and mortality (Allender et al., 2009; Office for National Statistics, 2017). Chapter 5 has now also found that health literacy and cognitive ability both uniquely contribute to risk of diabetes, a common chronic disease known to increase the risk of mortality (Diabetes UK, 2014). The next chapter will test whether health literacy and cognitive ability predict mortality.

6. Health literacy, cognitive ability, and mortality

6.1. Introduction

Chapters 4 and 5, respectively, examined the relationship between health literacy and cognitive ability with smoking and diabetes. These studies found that, when health literacy and cognitive ability were included concurrently as exposures in a regression model, both health literacy and cognitive ability had independent associations with smoking and diabetes. The studies reported in Chapters 4 and 5 used data from ELSA. An advantage of the ELSA sample is that it is a large and representative sample of middle-aged and older adults living in England. One limitation, however, is that the health literacy and cognitive ability measures used in ELSA are relatively brief. The health literacy test used in Chapters 4 and 5 was a four-item test of health-related reading comprehension. The cognitive ability measure consisted of a composite score based on performance on four brief tests of memory, processing speed and executive function. Many other cognitive domains, including reasoning and working memory (Section 2.2), which are known to load highly on general cognitive ability (Section 2.3.1; Salthouse, 2004) were not included in the ELSA composite cognitive ability score.

It is possible that some of the independent contribution of health literacy on smoking and diabetes status reported in Chapters 4 and 5 could be residual cognitive skills not being captured by the brief cognitive ability measure used in these chapters. To better understand whether health literacy and cognitive ability have independent associations with health, samples with more detailed tests of cognitive ability and health literacy are needed. Using data from the Lothian Birth Cohort 1936 (LBC1936) study (Deary, Gow, et al., 2007; Deary et al., 2012; A. M. Taylor, Pattie,

& Deary, 2018), this chapter examines whether health literacy has unique associations with mortality that are independent of cognitive ability. One strength of the LBC1936 sample's dataset is that a comprehensive cognitive assessment, including a number of tests from the WAIS III (Section 2.2.1), has been administered to these participants on five different occasions in old age. This detailed cognitive assessment enables the creation of a more comprehensive cognitive ability measure than that created using ELSA data. Three commonly-used health literacy tests—the REALM, the S-TOFHLA, and the Newest Vital Sign (Section 1.3)—were also administered to LBC1936 participants during the second wave of testing. In addition to information on older age cognitive ability and health literacy, most of the LBC1936 participants also completed a validated test of intelligence when they were aged 11 years (Deary, Gow, et al., 2007; Deary et al., 2012; A. M. Taylor et al., 2018).

Therefore, LBC1936 is unusually well-suited for investigating the role of both current cognitive ability in older age, and prior cognitive ability—measured by performance on an intelligence test in childhood—in the association between health literacy and health. Using the LBC1936 sample, one study (Mõttus et al., 2014) has already examined the role of childhood cognitive ability and fluid cognitive ability in older age in the association between health literacy and physical health. That study (Mõttus et al., 2014) found that cognitive ability largely attenuated the association between health literacy and physical health in older age (the results of this study are described in detail in Section 3.4). It did not study mortality; at that time, relatively few of the LBC1936 participants had died. The present chapter will examine the role of childhood cognitive ability and older age fluid cognitive ability in the association between health literacy and mortality.

This study has been published in *BMJ Open*, and the published paper is included in Section 6.2. The supplementary material for this paper is included in Appendix 2.

6.2. Role of cognitive ability in the association between functional health literacy and mortality in the Lothian Birth Cohort 1936: a prospective cohort study

BMJ Open

Role of cognitive ability in the association between functional health literacy and mortality in the Lothian Birth Cohort 1936: a prospective cohort study

Chloe Fawns-Ritchie,[1,2] John M Starr,[1,3] Ian J Deary[1,2]

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[1]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
[2]Department of Psychology, University of Edinburgh, Edinburgh, UK
[3]Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK

Correspondence to
Professor Ian J Deary; i.deary@ed.ac.uk

ABSTRACT

Objectives We investigated the role that childhood and old age cognitive ability play in the association between functional health literacy and mortality.
Design Prospective cohort study.
Setting This study used data from the Lothian Birth Cohort 1936 (LBC1936) study, which recruited participants living in the Lothian region of Scotland when aged 70 years, most of whom had completed an intelligence test at age 11 years.
Participants 795 members of the LBC1936 with scores on tests of functional health literacy and cognitive ability in childhood and older adulthood.
Primary and secondary outcome measures Participants were followed up for 8 years to determine mortality. Time to death in days was used as the primary outcome measure.
Results Using Cox regression, higher functional health literacy was associated with lower risk of mortality adjusting for age and sex, using the Shortened Test of Functional Health Literacy in Adults (HR 0.95, 95% CI 0.92 to 0.98), the Newest Vital Sign (HR 0.88, 95% CI 0.80 to 0.97) and a functional health literacy composite measure (HR 0.77, 95% CI 0.65 to 0.92), but not the Rapid Estimate of Adult Literacy in Medicine (HR 0.95, 95% CI 0.90 to 1.01). Adjusting for childhood intelligence did not change these associations. When additionally adjusting for fluid-type cognitive ability in older age, associations between functional health literacy and mortality were attenuated and non-significant.
Conclusions Current fluid ability, but not childhood intelligence, attenuated the association between functional health literacy and mortality. Functional health literacy measures may, in part, assess fluid-type cognitive abilities, and this may account for the association between functional health literacy and mortality.

Strengths and limitations of this study

- This study used three functional health literacy tests, which enabled us to create a composite functional health literacy measure.
- This study had comprehensive tests of cognitive ability measured in both childhood and old age which allowed us to investigate whether childhood and old age cognitive ability independently played a role in the relationship between functional health literacy and mortality.
- The health literacy measures used here only assessed functional health literacy, and therefore, we cannot determine whether cognitive ability would attenuate the association between health literacy and mortality if we used multidimensional health literacy measures.
- Larger samples and a longer follow-up time are needed to determine the role of cognitive ability in the association between functional health literacy and cause-specific mortality.

INTRODUCTION

Health literacy is "the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make basic health decisions".[1] This ability is thought to be multifaceted and encompasses the set of skills required to navigate the healthcare environment.[2–4] One component of health literacy is functional health literacy—the reading, writing and numeracy skills required to understand health information.[3 5 6] Tests designed to assess functional health literacy have been developed to measure health-related reading and numeracy skills, such as the commonly used Test of Functional Health Literacy in Adults.[5 6] This test requires participants to read materials often used in the healthcare setting, such as a medicine bottle, and answer questions about these materials.

Performance on functional health literacy tests has been associated with a range of health outcomes. Individuals with lower functional health literacy are more likely to require emergency care and have poorer skills in relation to correctly taking medication and interpreting written health materials.[7] Individuals with higher functional health literacy are more likely to take part in health-promoting behaviours, such as eating a healthy diet, and are more likely to take part in routine cancer screening.[8 9]

Successful completion of functional health literacy measures relies on cognitive functions, such as processing capacity and reasoning.[10 11] One dominant theory in intelligence research is that there is a distinction between fluid ability, the ability to problem solve using novel material, which tends to decline with increasing age, and crystallised ability, which is the knowledge acquired throughout life which remains relatively stable across the lifespan.[12–16] Successful completion of tests of functional health literacy likely requires both crystallised abilities, such as specific knowledge relating to health, and fluid abilities, such as reasoning.[10 11] It is therefore unsurprising that performance on tests of functional health literacy and cognitive function are strongly related.[17–24] Some tests of functional health literacy have been found to correlate more strongly with measures of cognitive ability than with each other.[23 25 26] This overlap is so strong that some have proposed that functional health literacy should not be considered a unique construct but, instead, should be thought of as a specific component of cognitive function.[26]

Given the association between performance on tests of functional health literacy and cognitive ability tests, researchers have investigated whether the relationship between functional health literacy and health remains when also measuring cognitive ability. Whereas most evidence suggests that cognitive function explains a large proportion of the association between functional health literacy and health, the degree of attenuation varies.[25 27 28] A study using participants from the Lothian Birth Cohort 1936 (LBC1936)[25] —the same sample used in the current study—investigated whether cognitive ability in childhood and late adulthood attenuated the association between functional health literacy and physical health. In models without cognitive function, functional health literacy was associated with all three of the measures of physical health assessed. Addition of cognitive ability in older age significantly attenuated the association between functional health literacy with physical fitness by 43% and number of natural teeth by 39%; however, it did not attenuate the association between functional health literacy and body mass index (BMI). Conversely, whereas childhood cognitive ability did not attenuate the association between functional health literacy and physical fitness, it attenuated the association between functional health literacy and number of teeth by 30% and BMI by 88%. In the fully adjusted model which included childhood and late adulthood cognitive ability, as well as other early-life factors, the association between functional health literacy and physical fitness, though attenuated by 43%, remained significant,[25] suggesting that functional health literacy may play a small but unique role in physical fitness.

Mortality is arguably one of the most important health outcomes to examine. Both cognitive ability[29 30] and functional health literacy[31] have been found to predict mortality. Researchers have therefore investigated the degree to which cognitive function explains the association between functional health literacy and mortality. When not controlling for cognitive function, Baker *et al*[32] found that individuals with inadequate compared with adequate health literacy had a 50% higher risk of dying. When additionally adjusting for cognitive function, the risk reduced to 27%, but remained significant. A similar pattern of attenuation was found in another study.[33] Thus, cognitive function did not fully explain this relationship. These two studies, however, used brief measures of functional health literacy and cognitive function.

The present study sought to better understand the relationship between functional health literacy, cognitive ability and mortality using data from the LBC1936. We note that this is the same sample as used in Mõttus *et al*[25] to investigate the association between functional health literacy, cognitive ability and physical health. In this previous study,[25] physical health was measured concurrently with fluid ability and functional health literacy. The current analysis is different from and complementary to this previous study in that we followed up the participants for 8 years to determine mortality status—obviously a most important health outcome. Studies that have examined the role that cognitive function plays in the association between functional health literacy and mortality used brief cognitive measures collected at the same time as the functional health literacy tests.[32 33] It is not known whether early-life cognitive ability and cognitive ability in older age play different roles in the association between health literacy and mortality. The current analysis utilises cognitive test scores collected in childhood, which are thought to measure the trait of lifelong intelligence, and current cognitive ability in older age, measured at approximately 73 years and contemporaneously with functional health literacy. The aim of this study was to determine whether childhood cognitive ability and current cognitive ability in older adulthood play unique roles in the association between functional health literacy and mortality.

METHODS

Participants

LBC1936 is a cohort study of 1091 older adults born in 1936, most of whom reside in the Lothian area in Scotland. Most had taken part in the Scottish Mental Survey 1947, which tested the intelligence of almost all children born in 1936 and attending Scottish schools on 4 June 1947.[34] LBC1936 consists of a sample of these individuals who were subsequently followed up, for the first time, at age 70 years (wave 1). To date, these participants have been followed up a further three times at approximately 3-year intervals (waves 2–4). LBC1936 was designed principally to investigate healthy, non-pathological, cognitive ageing. Detailed information on this cohort is provided

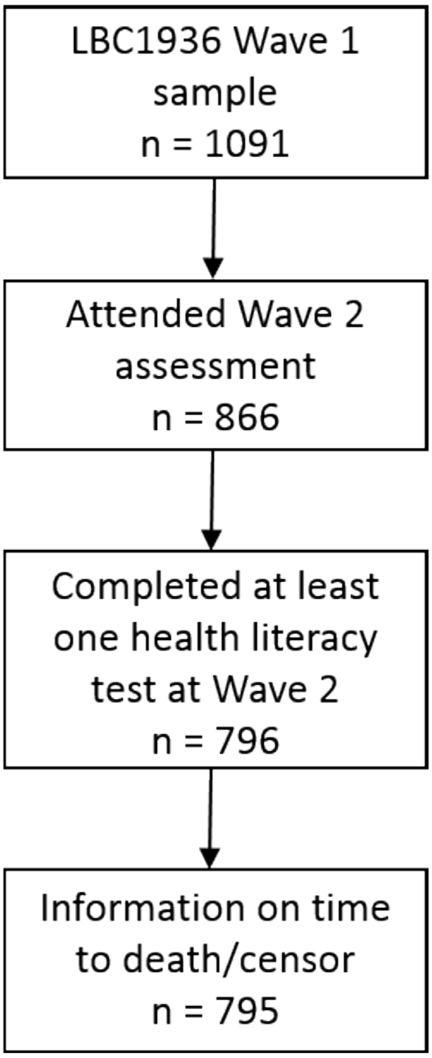

Figure 1 Flow diagram of the sample used to investigate the role of cognitive ability in the association between health literacy and mortality (n=795). LBC1936, Lothian Birth Cohort 1936.

elsewhere.[35 36] The present study used a subsample of 795 (413 male and 382 female) LBC1936 participants who completed tests of health literacy at wave 2 when participants were approximately aged 73 years. Figure 1 shows a flow chart of how the analytic sample for this current study was derived.

Written informed consent was obtained from participants. This study conformed to the principles embodied in the Declaration of Helsinki.

Measures

Mortality and survival time

The General Register Office for Scotland was used to identify deaths. Deaths through the end of March 2017 were recorded, and this date is used as the censoring date for participants who survived. Survival time was measured in days from date of attending study visit at wave 2 to date of death or censoring date.

Functional health literacy

Three functional health literacy tests were administered at wave 2.

Rapid Estimate of Adult Literacy in Medicine (REALM)[37]: This test measures participants' ability to read and correctly pronounce medical words. Participants are presented a piece of paper with a list of 66 medical words and are asked to read these words aloud. The words range in difficulty from easy ('fat') to difficult ('impetigo'). One point is given for each correctly pronounced word. One week test–retest (r=0.99)[37] and internal consistency (Cronbach's alpha=0.98)[38] have been found to be very high.

Shortened Test of Functional Health Literacy in Adults (S-TOFHLA)[5 6]: In the numeracy section, participants are provided with cards with medical information on them and are asked four questions about this information. The reading comprehension section comprised a 36-item task which involved participants reading two health-related passages where every fifth to seventh word was missing, and participants were to select the missing word from four options. Participants had 12 min to complete both sections. Here, the British version of the S-TOFHLA[9] was used which substitutes the Medicaid passage for a passage about UK prescription fee exemptions. This measure is a shortened version of the Test of Functional Health Literacy in Adults, which is seen as the gold standard functional health literacy test.[39] Successful completion of the S-TOFHLA requires the ability to read and comprehend written words and numbers in a health context. Internal consistency is high for reading comprehension (Cronbach's alpha=0.97)[6] and adequate for numeracy (Cronbach's alpha=0.68).[6] The S-TOFHLA has been found to correlate strongly with the REALM (r=0.80).[6]

Newest Vital Sign (NVS)[40]: Participants were presented with a nutrition label from a container of ice cream and were asked to answer six questions about the information provided on this label. The NVS assesses both reading comprehension and numeracy skills associated with health as participants need to use the written text and numbers on the label to answer the questions.[40] The NVS correlates with the S-TOFHLA at r=0.59[40] and shows reasonable internal consistency (Cronbach's alpha=0.76).[40]

General health literacy: The three functional health literacy measures used here have been found to correlate moderately with each other.[25] To capture the shared variance between these tests, a general measure of functional health literacy was created by entering scores on the three tests into a principal component analysis (PCA). Two of these measures had skewed distributions (see online supplementary figures 1–8); therefore, Spearman's rank correlation was used in the PCA. Only the first component had an eigenvalue >1, and the scree slope indicated a single component; therefore, scores from the first unrotated principal component were used as a composite of functional health literacy (general functional health literacy). This component accounted for 59.7% of the total variance, confirming that there was substantial shared variance between the three functional health literacy tests. The REALM, S-TOFHLA and NVS loaded 0.74, 0.80 and 0.77, respectively, on this component.

Cognitive ability

Childhood cognitive ability (age-11 IQ)

As part of the Scottish Mental Survey 1947, almost all 11-year-old children in Scotland in 1947 sat the Moray House Test No. 12 (MHT),[34] a 45-minute, group-administered intelligence test that included tasks of verbal reasoning and spatial ability and had a maximum score of 76. In LBC1936, scores on the MHT were adjusted for age in days at testing and then were converted into standard IQ-type scores with a mean of 100 and an SD of 15. This score will be used as a measure of prior, or crystallised, ability.

Current fluid ability

Participants completed a lengthy cognitive assessment.[35 36] As has been done in previous LBC1936 studies,[23 25] six tests administered at wave 2 thought to measure fluid-type cognitive abilities that tend to decline across the lifespan[14–16] were entered into a PCA. The following tests from the Wechsler Adult Intelligence Scale—III[41] that assess non-verbal reasoning, visuospatial ability, working memory and processing speed were used: Matrix Reasoning, Block Design, Letter–Number Sequencing, Symbol Search, Digit Span Backwards and Digit Symbol-Coding. Only the first component had an eigenvalue >1, and the scree slope indicated one component, and therefore, scores from this first principal component were used as a measure of current fluid ability. This component accounted 50.2% of the total variance. The loadings for the six tests were: Matrix Reasoning=0.69, Block Design=0.71, Letter–Number Sequencing=0.71, Symbol Search=0.75, Digit Span Backwards=0.64 and Digit Symbol-Coding=0.75.

Covariates

Sociodemographic variables included in this analysis were education and occupational social class. Years of full-time education completed, recorded at wave 1 when participants were aged 70 years, was used to measure education. At wave 1, participants were assigned to one of the following occupational social classes based on their highest occupational status prior to retirement[42]: professional, managerial and technical, skilled, partly skilled manual and unskilled manual. Female participants were assigned the occupational class of their husband if this was higher than their own. Skilled was separated into skilled non-manual and skilled manual. Only five participants in this sample were assigned the occupational class of unskilled; therefore, partly skilled manual and unskilled manual were combined into one class, hereafter referred to as manual (n=31).

Three measures of health status measured at wave 2 were used. Self-reported health was measured by asking participants whether they rated their general health to be excellent, very good, good, fair or poor. Only a small number of participants who were recorded dead at the censoring date reported poor (n=3) or excellent (n=17) health. Therefore, poor and fair were collapsed into one category (fair/poor; n=73), as were very good and excellent (very good/excellent; n=487). Total score on the Hospital Anxiety and Depression Scale (HADS)[43] was used as a measure of mood state. Higher scores on the HADS represent higher levels of anxiety and depression. Activities of daily living were assessed using the Townsend Disability Scale.[44] Participants were given a score of 0 (no difficulty completing this activity) to 2 (not able to complete this activity) for nine activities, and thus higher scores represent more functional disability.

Patient and public involvement

LBC1936 participants were not involved in the development of any part of this study. The results will be disseminated to participants via a quarterly newsletter sent to LBC1936 participants.

Statistical analysis

SPSS V.21.0 was used to carry out this analysis. To determine whether those recorded as alive or dead at censoring date differ on demographic, functional health literacy, cognitive function or health status variables, X^2 tests were conducted for categorical variables, independent t-tests were used for normally distributed continuous variables and Mann-Whitney U tests were used for non-normal continuous variables. Spearman's rank-order correlation was used to examine the relationship between functional health literacy and cognitive ability scores. To investigate the association between functional health literacy and time to death, Cox proportional hazard regression was used. For each of the functional health literacy measures of interest (REALM, S-TOFHLA, NVS and the composite score of general functional health literacy), six models were run. In Model 1, the functional health literacy measure of interest and age and sex was entered. Years of education was added in Model 2 as this has been found to be associated with functional health literacy. To determine whether cognitive ability in childhood attenuated the association between functional health literacy and mortality, age-11 IQ was added (Model 3). In Model 4, fluid-type cognitive ability in older age was additionally added to determine its role in the association between functional health literacy and mortality. Occupational class was additionally included in Model 5. Finally, health status variables (self-reported health, HADS and Townsend) were included in Model 6. Methods to control for multiple testing were not used here. We were interested in the change in the effect size of the association between functional health literacy and mortality following the inclusion of various cognitive, sociodemographic and health variables. In the Results section of the main text here, only the HRs and 95% CIs for the functional health literacy measures are reported. A more detailed

Table 1 Participant characteristics for participants alive or dead at censoring date and p values to determine whether these characteristics differed by survival status

	n	Alive	Dead	P values
Survival time (years), mean (SD)	795	8.19 (0.66)	5.23 (2.14)	
Age (years) at wave 2, mean (SD)	795	72.54 (0.70)	72.41 (0.72)	0.068
Sex, n (%)	795			0.069
Male		336 (50.5)	77 (59.2)	
Female		329 (49.5)	53 (40.8)	
Years of education, mean (SD)	795	10.80 (1.16)	10.71 (1.10)	0.417
Occupational class, n (%)	780			0.001
Professional		142 (21.7)	12 (9.4)	
Managerial/technical		249 (38.1)	49 (38.6)	
Skilled: non-manual		140 (21.4)	26 (20.5)	
Skilled: manual		96 (14.7)	35 (27.6)	
Manual		26 (4.0)	5 (3.9)	
Self-reported health, n (%)	795			<0.001
Poor/fair		47 (7.1)	26 (19.9)	
Good		195 (29.4)	40 (30.5)	
Very good/excellent		422 (63.5)	65 (49.6)	
HADS total, mean (SD)	794	7.02 (4.37)	7.42 (4.62)	0.342
Townsend Disability Scale, mean (SD)	794	0.89 (1.82)	1.60 (2.48)	0.001

HADS, Hospital Anxiety and Depression Scale.

description of the results for all variables in the models is given in the online supplementary materials.

RESULTS

A total of 796 participants completed the functional health literacy measures at wave 2 (figure 1). Following removal of one participant without information on date of death, 130 participants had died, and 665 participants were alive at the censoring date. Participant characteristics are reported in table 1, and functional health literacy and cognitive ability scores are shown in table 2. Those who died were more likely to be from a lower occupational class, were more likely to report poorer health and reported more disability than those who survived. Participants who had died had lower scores on all the functional health literacy measures and had lower fluid cognitive ability scores in older age. Age-11 IQ did not differ between the two groups.

Table 2 Mean scores (SD) on measures of functional health literacy and cognitive ability by survival status and p values to determine whether these scores differ by survival status

	n	Alive	Dead	P values
REALM score	794	65.08 (2.39)	64.67 (3.02)	0.015
S-TOFHLA score	744	38.00 (3.85)	36.69 (5.37)	0.025
NVS score	789	2.92 (1.90)	2.48 (1.92)	0.011
General functional health literacy	740	0.05 (0.98)	−0.24 (1.08)	0.007
Age-11 IQ	752	101.08 (14.99)	98.55 (16.33)	0.091
Current fluid ability	789	0.07 (0.99)	−0.34 (1.00)	<0.001

NVS, Newest Vital Sign; REALM, Rapid Estimate of Adult Literacy in Medicine; S-TOFHLA, Shortened Test of Functional Health Literacy in Adults.

Table 3 shows the rank-order correlations between functional health literacy and cognitive ability measures. These have been reported elsewhere.[23 25] The three functional health literacy measures correlated moderately with each other (r=0.35–0.44, p<0.001), and higher scores on the functional health literacy measures were correlated with higher age-11 IQ (r=0.44–0.51, p<0.001) and higher fluid ability (r=0.38–0.55, p<0.001). The three functional health literacy measures tended to correlate more strongly with measures of cognitive ability than with each other. The general functional health literacy measure also showed a strong positive correlation with both age-11 IQ (r=0.61, p<0.001) and fluid ability in older age (r=0.63, p<0.001). The correlations between all variables examined in this analysis are reported in online supplementary table 1.

The HRs for the association between functional health literacy and mortality are shown in table 4. HRs for all variables entered into the models are reported in online supplementary tables 2–5. In all models, the assumptions of proportional hazards were met. Given the high correlations between functional health literacy and cognitive

Table 3 Rank-order correlations between functional health literacy and cognitive ability measures

	1	2	3	4	5	6
1 REALM	–					
2 S-TOFHLA	0.40*	–				
3 NVS	0.35*	0.44*	–			
4 General functional health literacy	0.71*	0.80*	0.78*	–		
5 Age-11 IQ	0.44*	0.48*	0.51*	0.61*	–	
6 Current fluid ability	0.38*	0.55*	0.55*	0.63*	0.57*	–

*P<0.001.
NVS, Newest Vital Sign; REALM, Rapid Estimate of Adult Literacy in Medicine; S-TOFHLA, Shortened Test of Functional Health Literacy in Adults.

ability, variance inflation factors (VIFs) were calculated to check for multicollinearity. VIF values for all models were low (highest VIF=2.15), suggesting that there was no multicollinearity in these models.

REALM

The HRs for the REALM represent the risk of dying for a one-point increase in the REALM (max score=66). The REALM did not significantly predict mortality in Model 1 (HR 0.95, 95% CI 0.90 to 1.01) adjusting for age and sex or subsequently with the addition of education (Model 2), age-11 IQ (Model 3), fluid ability (Model 4), occupational class (Model 5) or health status (Model 6).

S-TOFHLA

The HRs for the S-TOFHLA represent the risk of mortality for a one-point increase in S-TOFHLA score (max score=40). With age and sex controlled for, a one-point increase in S-TOFHLA reduced the risk of dying by 5% (Model 1 HR 0.95, 95% CI 0.92 to 0.98). Inclusion of education (Model 2) and age-11 IQ (Model 3) did not attenuate this association. This association was attenuated and became non-significant in Model 4 with the inclusion of fluid ability (HR 0.97, 95% CI 0.93 to 1.01) and remained non-significant and continued to reduce in size following the addition of occupational class (Model 5) and health status (Model 6).

NVS

The HRs for NVS represent the risk of mortality for a one-point increase in NVS score (max score=6). In Model 1, in which age and sex were entered as covariates, NVS significantly predicted mortality. A one-point increase in NVS score reduced the risk of dying by 12% (HR 0.88, 95% CI 0.80 to 0.97). The addition of years of education (Model 2) did not attenuate this association. Age-11 IQ was added in Model 3, and this did little to change the association between NVS and mortality. The inclusion of fluid ability in Model 4 greatly attenuated the association between NVS and mortality, and this association became non-significant (HR 0.96, 95% CI 0.86 to 1.08). This association remained non-significant following the inclusion of occupational class (Model 5) and health status variables (Model 6).

General functional health literacy

The HRs for general functional health literacy represent the risk of mortality for a one SD increase in general functional health literacy. General functional health literacy predicted mortality in Model 1, controlling for age and

Table 4 HRs (95% CIs) for the association between four measures of functional health literacy and mortality, controlling for sociodemographic, cognitive and health variables

	Model 1 Age and sex	Model 2 +education	Model 3 +age-11 IQ	Model 4 +current fluid ability in older age	Model 5 +occup class	Model 6 +health status
REALM	0.95 (0.90 to 1.01) n=794	0.96 (0.90 to 1.01) n=794	0.96 (0.90 to 1.02) n=752	0.97 (0.91 to 1.04) n=746	0.97 (0.90 to 1.04) n=731	1.00 (0.92 to 1.07) n=728
S-TOFHLA	0.95 (0.92 to 0.98)** n=744	0.95 (0.92 to 0.98)** n=744	0.95 (0.91 to 0.98)** n=702	0.97 (0.93 to 1.01) n=697	0.98 (0.94 to 1.02) n=682	1.00 (0.95 to 1.05) n=680
NVS	0.88 (0.80 to 0.97)** n=789	0.88 (0.80 to 0.97)* n=789	0.89 (0.80 to 0.99)* n=746	0.96 (0.86 to 1.08) n=742	0.97 (0.86 to 1.09) n=727	0.96 (0.85 to 1.08) n=724
General functional health literacy	0.77 (0.65 to 0.92)** n=740	0.75 (0.61 to 0.90)** n=740	0.74 (0.59 to 0.93)* n=698	0.87 (0.67 to 1.13) n=694	0.911 (0.70 to 1.19) n=679	0.95 (0.72 to 1.25) n=677

*P<0.05, **p<0.01.
NVS, Newest Vital Sign; occup class, occupational class; REALM, Rapid Estimate of Adult Literacy in Medicine; S-TOFHLA, Shortened Test of Functional Health Literacy in Adults.

sex. A one SD increase in general functional health literacy reduced the risk of mortality by 23% (HR 0.77, 95% CI 0.65 to 0.92). Including years of education in Model 2 and age-11 IQ in Model 3 did little to change the association between general functional health literacy and mortality. Current fluid ability was included in Model 4, and this attenuated the association between general functional health literacy and mortality, and this association was no longer significant (HR 0.87, 95% CI 0.67 to 1.13). Adding occupational social class in Model 5 did little to change the association between general functional health literacy and mortality. Health status variables were added in Model 6, and the association between general functional health literacy and mortality was further attenuated and remained non-significant.

All models were rerun using only participants who had complete data on all of the variables of interest. These models are shown in online supplementary tables 6–9. The associations between functional health literacy and mortality were similar to those reported here, except that, in Model 1 for the REALM (online supplementary table 6), higher scores on the REALM significantly reduced the risk of mortality. This association was no longer significant in Model 2, following the inclusion of age-11 IQ.

Sensitivity analyses

Participants who may have a dementia or possible pathological cognitive impairment were not removed prior to running these analyses. One participant self-reported a diagnosis of dementia at the wave 2 assessment. Five participants in this sample have Mini-Mental State Examination scores below the often used cut-off of 24[45] (one participant scored 20/30, one scored 22/30 and three scored 23/30), which suggests a possible cognitive impairment. To determine whether the presence of dementia or possible cognitive impairment affects the results, these analyses were rerun excluding these six individuals. All associations were very similar to those reported above (results not shown; available from the authors), and therefore, the presence of dementia or possible cognitive impairment did not affect the main results.

DISCUSSION

This study investigated whether prior cognitive ability measured in childhood and current fluid cognitive ability measured in older adulthood played different roles in the association between functional health literacy and mortality. Three measures of functional health literacy were used; the REALM, S-TOFHLA and NVS. These three measures were also used to create a composite measure of functional health literacy. The REALM, a test that requires only the ability to read and correctly pronounce medical words, did not predict mortality, even in minimally adjusted models (though it had a slightly stronger and significant association when only those with full data were included, as shown in online supplementary analysis). When using functional health literacy tests that assessed reading comprehension and numeracy (S-TOFHLA, NVS and general functional health literacy), functional health literacy predicted mortality in models adjusting for age, sex and education only. Individuals who had higher scores on the S-TOFHLA, NVS and general functional health literacy had a lower risk of mortality than those with lower scores. Accounting for prior intelligence measured in childhood did not change this association. The association between functional health literacy and mortality disappeared when contemporaneous fluid ability was accounted for. The attenuation was particularly large for the NVS and general functional health literacy.

Two previous studies used functional health literacy tests that measure reading comprehension and numeracy to investigate the role that cognitive function plays in the association between functional health literacy and mortality.[32 33] These studies measured cognitive function concurrently with health literacy in middle-age or older adulthood and found that, although the size of the association between functional health literacy and mortality was reduced, functional health literacy still predicted mortality when cognitive function was controlled for.[32 33] We investigated the role that both childhood cognitive ability and cognitive ability in older age have on the association between functional health literacy and mortality. Here, fluid ability, but not childhood intelligence, attenuated the association between functional health literacy and mortality such that the association was no longer significant. Childhood cognitive ability, which was measured decades prior to the functional health literacy assessment, is thought to reflect the relatively stable trait of lifelong intelligence, whereas current fluid ability, which was measured when participants were approximately 73 years old, is a measure of current cognitive competence.[23] These results suggest that, whereas childhood intelligence did not play a role in the association between functional health literacy and mortality, current fluid-type cognitive ability in older adulthood accounted for a large proportion of this association.

A strength of this current study is that detailed measures of cognitive ability were used. Childhood intelligence was measured using a standardised test of intelligence which had good concurrent validity with other intelligence tests.[35] The fluid ability measure comprised many standardised neuropsychological tests. Both Baker *et al*[32] and Bostock and Steptoe[33] used brief measures of cognitive function. Baker *et al*[32] used specific items from the Mini-Mental State Examination, a measure designed to screen for cognitive impairment[45] which is insensitive to individual differences in healthy cognitive ageing. Bostock and Steptoe[33] used three brief cognitive tests administered in a non-standardised way in the participants' own home. These studies may not have used tests sensitive enough, or that covered a necessary range of cognitive functions, to fully account for the association between health literacy and mortality.

Another advantage of the current study is the use of three different tests of functional health literacy. All tests were used to measure functional health literacy; however, each test required the participant to carry out different health-related tasks. Whereas the REALM required the participant only to read and correctly pronounce words, the S-TOFHLA and NVS are more cognitively demanding tasks that assessed both reading comprehension and numeracy skills. Using these three measures enabled us to investigate whether different patterns of association between functional health literacy and mortality were found when using the different tests. By using three measures of functional health literacy, we were also able to create a composite measure of functional health literacy. This general measure was derived with the aim of creating a score that captures the shared variance between the three functional health literacy tests, providing a more comprehensive measure of functional health literacy.

The results of this study support the proposal by Reeve and Basalik[26] that functional health literacy may not be a unique construct; instead, it is tenable that tests of functional health literacy may in fact be largely measuring cognitive ability. First, we found, as has been reported elsewhere,[23 25] that tests of health literacy tended to correlate more strongly with tests of cognitive ability than with each other. The original paper describing the S-TOFHLA found that this test correlated with the REALM at r=0.80,[6] suggesting that these tests are measuring the same underlying ability. However, other studies have found moderate correlations between these tests, similar to ours.[46] Second, we found that the NVS, S-TOFHLA and general functional health literacy no longer predicted mortality when accounting for fluid cognitive ability. The results of our study suggest that health literacy may not be independent of cognitive ability. This attenuation is likely to be because there is an overlap in the content of tests of fluid ability and the NVS and S-TOFHLA. The NVS and S-TOFHLA are cognitively demanding tasks that are likely to be substantially measuring fluid-type cognitive abilities, such as working memory and reasoning, that decline with increasing age.[15] Childhood cognitive ability did not attenuate the association between functional health literacy and mortality, suggesting that the NVS and S-TOFHLA are measuring current fluid-type cognitive capability in old age, and not lifelong intelligence. Current fluid ability in older age may be driving much of the association between functional health literacy and mortality largely because tests of functional health literacy are assessing mostly the same underlying abilities as measures of fluid ability.

Some researchers have questioned the validity of some of the functional health literacy tests used here. The Test of Functional Health Literacy in Adults is often reported as the gold standard functional health literacy test.[39] However, the NVS has been found to have poor concurrent validity with the Test of Functional Health Literacy in Adults.[39] In support of this, we found that the rank-order correlation between the NVS and S-TOFHLA was modest (r=0.44). Concerns have been raised about the fact that the REALM assesses only the ability to read and pronounce words.[38] Knowing how to pronounce medical words may not be directly related to the ability to understand medical information, and therefore, this may not adequately cover all the domains of functional health literacy.[38] Indeed, all the tests used here were designed to largely measure the component of health literacy known as functional health literacy. None of these measures assess other components of health literacy such as the skills required to critically analyse health information or the communicative skills needed to participate and navigate in the healthcare environment.[3] Assessments of health literacy that are designed to measure a much broader range of health literacy skills are available, such as the Health Literacy Questionnaire (HLQ)[47] and the European Health Literacy Survey Questionnaire (HLS-EU-Q).[48] The HLQ assesses nine dimensions of health literacy, including the ability to actively manage health and navigate the healthcare system.[47] Whereas the HLS-EU-Q measures self-reported skills in being able to access, understand, appraise and apply health-related information in the healthcare setting, as well as in disease prevention and health promotion.[48] Fluid cognitive ability may not play a role in the association between health literacy and mortality if we used these self-reported, broad, measures of health literacy, rather than the objective, but narrow, functional health literacy tests used here.

There are some limitations to this study. The LBC1936 participants were followed up for the first time at age 70 years, and therefore, the sample used in this analysis will likely suffer from a survival bias as this sample is made up of individuals who have survived to the age of 70 years. LBC1936 participants also tended to have higher scores on the MHT (age-11 IQ test) than Scottish-wide and Edinburgh-wide participants who also sat this test in 1947 as part of the Scottish Mental Survey.[36] Thus, individuals in this sample tended to be brighter than the original Scottish Mental Survey 1947 participants. This analysis only examined the association between functional health literacy and all-cause mortality. It is possible that there are different relationships between functional health literacy and cause-specific mortality, for example, functional health literacy may only predict deaths linked to unhealthy lifestyles, such as cardiovascular disease. The follow-up period in this study was relatively short, and therefore, only a small percentage of participants had died. Future studies should investigate mortality over a longer follow-up period and in larger samples to examine whether there are different patterns of association between functional health literacy and cause-specific mortality.

We investigated whether childhood cognitive ability and fluid ability in older age play independent roles in the association between functional health literacy and mortality. The results indicate that fluid-type cognitive capability may account for the association between functional health literacy and mortality, whereas childhood cognitive ability—an indicator of lifelong intelligence—does not. Researchers and clinicians should be aware that lower functional health literacy scores may actually reflect lower cognitive ability in older age, and that current cognitive capacity in older adulthood, but not lifelong intelligence, may be driving the association between functional health literacy and mortality. Future research examining the association between functional health literacy and mortality, and other health indicators, should also include measures of cognitive ability to be able to properly disentangle the relationship between functional health literacy and health.

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Contributors CF-R discussed and planned the study and analyses, analysed the data, interpreted the data and drafted the initial manuscript. JMS discussed and planned the study and analyses, interpreted the data and contributed to the manuscript. IJD discussed and planned the study and analyses, interpreted the data and contributed to the manuscript.

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REFERENCES

1. Institute of Medicine. *Health Literacy: a prescription to end confusion*. Washinton, DC: The National Academies Press, 2004.
2. Baker DW. The meaning and the measure of health literacy. *J Gen Intern Med* 2006;21:878–83.
3. Nutbeam D. Health literacy as a public health goal: a challenge for contemporary health education and communication strategies into the 21st century. *Health Promot Int* 2000;15:259–67.
4. Nutbeam D. The evolving concept of health literacy. *Soc Sci Med* 2008;67:2072–8.
5. Parker RM, Baker DW, Williams MV, *et al*. The test of functional health literacy in adults. *J Gen Intern Med* 1995;10:537–41.
6. Baker DW, Williams MV, Parker RM, *et al*. Development of a brief test to measure functional health literacy. *Patient Educ Couns* 1999;38:33–42.
7. Berkman ND, Sheridan SL, Donahue KE, *et al*. Low health literacy and health outcomes: an updated systematic review. *Ann Intern Med* 2011;155:97–107.
8. Kobayashi LC, Wardle J, von Wagner C. Limited health literacy is a barrier to colorectal cancer screening in England: evidence from the English Longitudinal Study of Ageing. *Prev Med* 2014;61:100–5.
9. von Wagner C, Knight K, Steptoe A, *et al*. Functional health literacy and health-promoting behaviour in a national sample of British adults. *J Epidemiol Community Health* 2007;61:1086–90.
10. Chin J, Morrow DG, Stine-Morrow EA, *et al*. The process-knowledge model of health literacy: evidence from a componential analysis of two commonly used measures. *J Health Commun* 2011;16 Suppl 3(Suppl 3):222–41.
11. Morrow D, Chin J. Decision Making and Health Literacy among Older Adults. In: Strough T, Löckenhoff C, eds. *Aging and decision making: empirical and applied perspectives*. London: Academic Press, 2015:261–82.
12. Cattell RB. Theory of fluid and crystallized intelligence: A critical experiment. *J Educ Psychol* 1963;54:1–22.
13. Horn JL. A basis for research on age differences in cognitive capabilities. In: McArdle JJ, Woodcock RW, eds. *Human cognitive abilities in theory and practice*. New York: Routledge, 1998:57–91.
14. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol* 2009;60:173–96.
15. Salthouse TA. Selective review of cognitive aging. *J Int Neuropsychol Soc* 2010;16:754–60.
16. Schaie KW. *Intellectual development in adulthood: the seattle longitudinal study*. Cambridge: Cambridge University Press, 1996.
17. Bennett JS, Boyle PA, James BD, *et al*. Correlates of health and financial literacy in older adults without dementia. *BMC Geriatr* 2012;12:30.
18. Dahlke AR, Curtis LM, Federman AD, *et al*. The mini mental status exam as a surrogate measure of health literacy. *J Gen Intern Med* 2014;29:615–20.
19. Federman AD, Sano M, Wolf MS, *et al*. Health literacy and cognitive performance in older adults. *J Am Geriatr Soc* 2009;57:1475–80.
20. Kobayashi LC, Wardle J, Wolf MS, *et al*. Cognitive function and health literacy decline in a cohort of aging english adults. *J Gen Intern Med* 2015;30:958–64.
21. Kobayashi LC, Smith SG, O'Conor R, *et al*. The role of cognitive function in the relationship between age and health literacy: a cross-sectional analysis of older adults in Chicago, USA. *BMJ Open* 2015;5:e007222.
22. Levinthal BR, Morrow DG, Tu W, *et al*. Cognition and health literacy in patients with hypertension. *J Gen Intern Med* 2008;23:1172–6.
23. Murray C, Johnson W, Wolf MS, *et al*. The association between cognitive ability across the lifespan and health literacy in old age: The Lothian Birth Cohort 1936. *Intelligence* 2011;39:178–87.
24. Ownby RL, Acevedo A, Waldrop-Valverde D, *et al*. Abilities, skills and knowledge in measures of health literacy. *Patient Educ Couns* 2014;95:211–7.
25. Mõttus R, Johnson W, Murray C, *et al*. Towards understanding the links between health literacy and physical health. *Health Psychol* 2014;33:164–73.
26. Reeve CL, Basalik D. Is health literacy an example of construct proliferation? A conceptual and empirical evaluation of its redundancy with general cognitive ability. *Intelligence* 2014;44:93–102.
27. O'Conor R, Wolf MS, Smith SG, *et al*. Health literacy, cognitive function, proper use, and adherence to inhaled asthma controller medications among older adults with asthma. *Chest* 2015;147:1307–15.
28. Serper M, Patzer RE, Curtis LM, *et al*. Health literacy, cognitive ability, and functional health status among older adults. *Health Serv Res* 2014;49:1249–67.
29. Murray C, Pattie A, Starr JM, *et al*. Does cognitive ability predict mortality in the ninth decade? The Lothian Birth Cohort 1921. *Intelligence* 2012;40:490–8.
30. Pavlik VN, de Moraes SA, Szklo M, *et al*. Relation between cognitive function and mortality in middle-aged adults: the atherosclerosis risk in communities study. *Am J Epidemiol* 2003;157:327–34.
31. Baker DW, Wolf MS, Feinglass J, *et al*. Health literacy and mortality among elderly persons. *Arch Intern Med* 2007;167:1503–9.
32. Baker DW, Wolf MS, Feinglass J, *et al*. Health literacy, cognitive abilities, and mortality among elderly persons. *J Gen Intern Med* 2008;23:723–6.
33. Bostock S, Steptoe A. Association between low functional health literacy and mortality in older adults: longitudinal cohort study. *BMJ* 2012;344:e1602.
34. Scottish Council for Research in Education. The trend of Scottish intelligence. In: *A comparison of the 1947 and 1932 surveys of intelligence of eleven-year-old pupils*. London, UK: University of London Press, 1949.
35. Deary IJ, Gow AJ, Taylor MD, *et al*. The Lothian Birth Cohort 1936: a study to examine influences on cognitive ageing from age 11 to age 70 and beyond. *BMC Geriatr* 2007;7:28.
36. Deary IJ, Gow AJ, Pattie A, *et al*. Cohort profile: the Lothian Birth Cohorts of 1921 and 1936. *Int J Epidemiol* 2012;41:1576–84.
37. Davis TC, Long SW, Jackson RH, *et al*. Rapid estimate of adult literacy in medicine: a shortened screening instrument. *Fam Med* 1993;25:391–5.

38. Dumenci L, Matsuyama RK, Kuhn L, *et al*. On the Validity of the Rapid Estimate of Adult Literacy in Medicine (REALM) Scale as a Measure of Health Literacy. *Commun Methods Meas* 2013;7:134–43.
39. Mancuso JM. Assessment and measurement of health literacy: an integrative review of the literature. *Nurs Health Sci* 2009;11:77–89.
40. Weiss BD, Mays MZ, Martz W, *et al*. Quick assessment of literacy in primary care: the newest vital sign. *Ann Fam Med* 2005;3:514–22.
41. Wechsler D. *WAIS-III UK administration and scoring manual*. London, UK: Psychological Corporation, 1998.
42. General Register Office. *Census 1951: classification of occupatioans*. London, UK, 1956.
43. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
44. Townsend P. *Poverty in the United Kingdom: a survey of household resources and standards of living*. Harmondsworth, UK: Penguin, 1979.
45. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
46. Jordan JE, Osborne RH, Buchbinder R. Critical appraisal of health literacy indices revealed variable underlying constructs, narrow content and psychometric weaknesses. *J Clin Epidemiol* 2011;64:366–79.
47. Osborne RH, Batterham RW, Elsworth GR, *et al*. The grounded psychometric development and initial validation of the Health Literacy Questionnaire (HLQ). *BMC Public Health* 2013;13:658.
48. Sørensen K, Van den Broucke S, Pelikan JM, *et al*. Measuring health literacy in populations: illuminating the design and development process of the European Health Literacy Survey Questionnaire (HLS-EU-Q). *BMC Public Health* 2013;13:948.

6.3. Conclusion

The present chapter investigated the role of childhood cognitive ability and older age fluid cognitive ability in the association between health literacy and mortality in the LBC1936 sample. The REALM did not predict mortality, even when only adjusting for age and sex. Higher scores on the S-TOFHLA, Newest Vital Sign, and a general measure of health literacy (created by entering the REALM, S-TOFHLA and Newest Vital Sign into a PCA and saving the scores on the first unrotated principal component) were associated with lower risk of mortality. Adjusting for childhood cognitive ability did not attenuate these associations. Additionally adjusting for fluid cognitive ability in older age attenuated the relationship between health literacy and mortality and neither S-TOFHLA, nor Newest Vital Sign, nor general health literacy were associated with mortality after adjusting for fluid ability in old age. Higher scores on fluid ability, on the other hand, were associated with lower risk of mortality.

In contrast to the results reported in Chapters 4 and 5, which found that both health literacy and cognitive ability were independently associated with health, the results reported in this chapter indicate that health literacy did not have associations with mortality that were independent of fluid cognitive ability in older adulthood. The findings reported in this chapter provide support for the suggestion that health literacy is not a unique construct, but is instead a subcomponent of cognitive ability (Mõttus et al., 2014; Reeve & Basalik, 2014). However, this broader, interesting issue—which will be discussed in Chapter 8—about the construct validity of health literacy cannot be settled in the present chapter or thesis.

One limitation of this study was that the LBC1936 participants were aged 73 at baseline and therefore the sample consisted of only participants who had survived to age 73 years. This study likely suffers from a survival bias. As the participants included in this study had survived to age 73 years, they are likely to be healthier than the general population, and they likely have better health literacy than the general population. Because this sample consisted of relatively healthy older adults, it is possible that a stronger relationship between health literacy and mortality would have been identified using a younger sample. In contrast to the results reported here, other studies, which have used younger participants, or participants with a wider age range, have found that higher health literacy is associated with reduced mortality, even after adjusting for cognitive ability (Baker et al., 2008; Bostock & Steptoe, 2012). Although the differences in results may be due to the fact these other studies used relatively brief tests of cognitive function (as discussed in Section 6.2), it is also possible that the differences in the age range of the samples used in these studies may have contributed to the differences in results. Future research should examine the attenuating role of cognitive ability in the association between health literacy and mortality using detailed tests of both health literacy and cognitive ability in samples who are younger than LBC1936 participants at the baseline assessment.

The first three empirical chapters (Chapters 4-6) of this thesis have examined the phenotypic associations between health literacy, cognitive ability and aspects of health. A complementary method to investigate the relationship between health literacy, cognitive ability and health would be to examine the genetic associations between these traits. The next chapter investigates whether the phenotypic associations reported in this thesis and elsewhere between health literacy, cognitive ability, and health variables are in part accounted for by genetic variants.

7. Genetic overlap between health literacy, cognitive ability, and health

7.1. Introduction

The literature reviewed in Chapters 1 to 3, and the empirical work reported in Chapters 4 to 6 highlight that health literacy, cognitive ability, and health variables are associated. Although these associations are reported widely, the mechanisms linking health literacy, cognitive ability, and health are poorly understood. One possibility is that the phenotypic associations between health literacy, cognitive ability, and health variables occur, in part, because these traits share some genetic architecture. The aim of this chapter is to investigate the shared genetic architecture of these traits.

Whereas, the genetic contributions to general cognitive ability and its genetic overlap with health variables have been reported (Section 2.4.5), the genetic variation in health literacy and the genetic overlap between health literacy, cognitive ability, and health has not been investigated. Using the ELSA sample, the present study investigates whether common genetic variants are associated with a measure of health literacy; it also tests whether common genetic variants previously found to be associated with cognitive ability and health-related traits are associated with performance on a test of health literacy.

This study has been published in *Twin Research and Human Genetics*, and the paper is included in Section 7.2. The supplementary material for this paper is included in Appendix 3.

7.2. Genetic contributions to health literacy

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Genetic Contributions to Health Literacy

Chloe Fawns-Ritchie[1,2], Gail Davies[1,2], Saskia P. Hagenaars[3] and Ian J. Deary[1,2,*]

[1]Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK, [2]Department of Psychology, University of Edinburgh, Edinburgh, UK and [3]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London, UK

Abstract

Higher health literacy is associated with higher cognitive function and better health. Despite its wide use in medical research, no study has investigated the genetic contributions to health literacy. Using 5783 English Longitudinal Study of Ageing (ELSA) participants (mean age = 65.49, *SD* = 9.55) who had genotyping data and had completed a health literacy test at wave 2 (2004–2005), we carried out a genome-wide association study (GWAS) of health literacy. We estimated the proportion of variance in health literacy explained by all common single nucleotide polymorphisms (SNPs). Polygenic profile scores were calculated using summary statistics from GWAS of 21 cognitive and health measures. Logistic regression was used to test whether polygenic scores for cognitive and health-related traits were associated with having adequate, compared to limited, health literacy. No SNPs achieved genome-wide significance for association with health literacy. The proportion of variance in health literacy accounted for by common SNPs was 8.5% (*SE* = 7.2%). Greater odds of having adequate health literacy were associated with a 1 standard deviation higher polygenic score for general cognitive ability [*OR* = 1.34, 95% CI (1.26, 1.42)], verbal-numerical reasoning [*OR* = 1.30, 95% CI (1.23, 1.39)], and years of schooling [*OR* = 1.29, 95% CI (1.21, 1.36)]. Reduced odds of having adequate health literacy were associated with higher polygenic profiles for poorer self-rated health [*OR* = 0.92, 95% CI (0.87, 0.98)] and schizophrenia [*OR* = 0.91, 95% CI (0.85, 0.96)). The well-documented associations between health literacy, cognitive function and health may partly be due to shared genetic etiology. Larger studies are required to obtain accurate estimates of SNP-based heritability and to discover specific health literacy-associated genetic variants.

Keywords: Health literacy; genome-wide association study; genetic; intelligence; education; health

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Health literacy is 'the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions' (Institute of Medicine, 2004). This capacity is thought to be important for navigating all aspects of health care, including the ability to seek out and act on appropriate health information and self-manage health conditions (Baker, 2006; Institute of Medicine, 2004). Tests of functional health literacy have been used to investigate the association between health literacy and health. Individuals with lower health literacy have been found to be less likely to take part in health-promoting behaviors (von Wagner et al., 2007). Lower health literacy is associated with poorer overall health status (Berkman et al., 2011), lower self-reported physical and mental health (von Wagner et al., 2007; Wolf et al., 2005) and greater self-reported depressive symptoms (Gazmararian et al., 2000). One study (Wolf et al., 2005) found that individuals with inadequate health literacy were 48% more likely to report a diagnosis of diabetes and 69% more likely to report having heart failure, compared to those with adequate health literacy, after adjusting for sociodemographic variables and health behaviors. Using prospective studies, lower health literacy predicted incident dementia (Kaup et al., 2014; Yu et al., 2017) and risk of dying (Baker et al., 2007; Berkman et al., 2011; Bostock & Steptoe, 2012).

Compared with those of health literacy, similar associations with health have been found for cognitive function. Individuals with higher cognitive function tend to participant more in health-promoting behaviors (Mons et al., 2013; Richards et al., 2003; Taylor et al., 2003; Wraw et al., 2018). Vascular risk factors, including diabetes and hypertension, have been associated with poorer cognitive function and greater cognitive decline (Knopman et al., 2009; Mõttus et al., 2013; Pavlik et al., 2005; Singh-Manoux & Marmot, 2005). Cognitive function, measured early in life, has been found to predict later life physical functioning and health status (Wraw et al., 2015), psychological distress (Gale et al., 2009), psychiatric illness (Batty et al., 2005; Dickson et al., 2012; Gale et al., 2008; Scult et al., 2017; Zammit et al., 2004), dementia (McGurn et al., 2008), and death (Batty et al., 2007; Calvin et al., 2011, 2017; Christensen et al., 2016).

Performance on tests of health literacy and cognitive function are moderately to highly correlated (Boyle et al., 2013; Mõttus et al., 2014; Murray et al., 2011; Reeve & Basalik, 2014). Murray et al. (2011) found that the correlations between general cognitive ability and three tests of health literacy, tested in older adulthood, ranged from .35 to .53 ($p < .001$). Given these correlations, researchers have sought to determine whether the relationship between health literacy and health remained when also accounting for cognitive function. Cognitive function has been consistently found to

Author for correspondence: Ian J. Deary, Email: ian.deary@ed.ac.uk
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attenuate the size of the association between health literacy and health; however, whereas some studies have found that health literacy no longer predicted better health when controlling for cognitive function (Fawns-Ritchie et al., 2018b; Mõttus et al., 2014; O'Conor et al., 2015; Serper et al., 2014), others have found that a small but significant association remained between higher health literacy scores and better health when also controlling for cognitive function (Baker et al., 2008; Bostock & Steptoe, 2012; Fawns-Ritchie et al., 2018a; Mõttus et al., 2014; Yu et al., 2017).

Whereas there is a wealth of evidence reporting a relationship between health literacy, cognitive function and health, it is less well understood why these associations are found. One possibility is that they share genetic influences. Cognitive function is substantially heritable (Deary et al., 2019; Haworth et al., 2010; Plomin & Deary, 2015). With increasing samples sizes, the specific genetic variants associated with cognitive function are being identified (Davies et al., 2018; Savage et al., 2018). One study (Hagenaars et al., 2016) sought to explore the shared genetic architecture between cognitive function and health, using two complementary genetic techniques: linkage disequilibrium (LD) score regression (Bulik-Sullivan et al., 2015) and polygenic profile scoring (Purcell et al., 2009). The first technique involves calculating the genetic correlations between two traits of interest using summary results from previous genome-wide association studies (GWAS). The second technique uses summary GWAS data for a specific trait (e.g., type 2 diabetes) and tests whether the genetic variants found to be associated with this trait are also associated with the same (e.g., type 2 diabetes) or a different (e.g., cognitive function) phenotype in an independent sample. Using these techniques, Hagenaars et al. (2016) found substantial shared genetic influences between cognitive function and physical and mental health. Negative genetic correlations were found between a test of verbal-numerical reasoning and Alzheimer's disease ($r_g = -0.39$, $p = .002$), and schizophrenia ($r_g = -0.30$, $p = 3.5 \times 10^{-11}$), among others. Polygenic profiles for various mental and physical health-related variables were associated with performance on tests of cognitive function, including coronary artery disease, Alzheimer's disease and schizophrenia. The shared genetic architecture between cognitive function and health has been subsequently replicated using larger samples (Davies et al., 2018).

Summaries are available regarding the advances made in understanding the genetic architecture of cognitive function and its overlap with physical and mental health (Deary et al., 2019; Hill, Harris et al., 2019). However, to the best of our knowledge, no one has investigated the genetic contributions to people's differences in health literacy. The aim of the present study was to explore the genetic contributions to health literacy and its overlap with cognitive function and health. Using data from the English Longitudinal Study of Ageing (ELSA), a sample of English adults aged 50 years and older, the present study conducted a GWAS of health literacy, estimated its single nucleotide polymorphism (SNP)-based heritability, and used polygenic profile scoring to examine the genetic overlap between health literacy and cognitive function, and health literacy and various health-related traits.

Materials and Methods

Participants

This study used data from ELSA (https://www.elsa-project.ac.uk/), a cohort study designed to be representative of English adults aged 50 years and older (Steptoe et al., 2013). The original sample (wave 1) was recruited in 2002–2003 and consisted of 11,391 participants. Participants have been followed up every 2 years and the sample has been refreshed at subsequent waves to ensure the sample's representativeness. Interviews took place via computer-assisted personal interviews and self-completion questionnaires in the participants' own homes. The topics assessed included health, financial and social circumstances. A nurse visit was carried out every second wave to measure biomarkers. Blood samples collected during the nurse visit have been used to genotype ELSA participants. More information on the ELSA sampling procedures are reported elsewhere (Steptoe et al., 2013). For the present study, a subsample of participants was used who completed the health literacy test at wave 2 (2004–2005) and who had genome-wide genotyping data ($n = 5783$).

Procedure

Health literacy. Health literacy was measured using a four-item reading and comprehension test. This test was designed to mimic written materials, such as drug labels, that would be encountered in a health-care setting. A piece of paper containing instructions for an over-the-counter packet of medicine was given to participants. Participants were asked four questions about the information on the medicine packet (e.g., 'What is the maximum number of days you may take this medication?'). One point was awarded for each correct answer. As has been done in other studies (Gale et al., 2015; Kobayashi et al., 2014), participants were categorized as having adequate (4/4 questions correct) or limited (<4 correct) health literacy.

Genotyping and quality control. A total of 7597 ELSA participants who had provided blood samples were genotyped in two batches (batch 1, $n = 5652$; batch 2, $n = 1945$) by UCL Genomics using the Illumina Omni 2.5-8 chip. Quality control procedures were performed by UCL Genomics and by the present authors. This included removal of SNPs based on call rate, minor allele frequency (MAF) and deviation from Hardy–Weinberg equilibrium. Individuals were removed based on call rate, relatedness, gender mismatch and non-Caucasian ancestry. A sample of 7358 participants remained following quality control procedures.

Imputation. Prephasing and imputation to the 1000 Genome Phase 3 reference panel (Altshuler et al., 2015) was performed using the Sanger Imputation Service (McCarthy et al., 2016), EAGLE2 (v2.0.5) (Loh et al., 2016) and PBWT (Durbin, 2014) pipeline.

Curation of summary results from GWAS of cognitive and health-related traits. Summary results from 21 GWAS of cognitive function, general health status variables, chronic diseases, health behaviors, neuropsychiatric disorders, years of schooling, social deprivation and the personality traits of conscientiousness and neuroticism were collected. For each trait, we checked the samples used in the GWAS to ensure ELSA was not included. Sources of summary statistics and key references are given in the Supplementary materials and Supplementary Table S1.

Statistical Analyses

Genome-wide association analyses. SNP-based association analyses were performed using the BGENIE v1.2 analysis package (https://jmarchini.org/bgenie/). A linear SNP association model was tested which accounted for genotype uncertainty. Prior to these analyses, the health literacy phenotype was adjusted for the following covariates: age, sex and 15 genetic principal components.

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Genomic risk loci characterization using FUMA. Genomic risk loci were defined from the SNP-based association results, using FUnctional Mapping and Annotation of genetic associations (FUMA; Watanabe et al., 2017). First, independent significant SNPs were identified using the SNP2GENE function and defined as SNPs with a p value of $< 1 \times 10^{-5}$ and independent of other genome-wide suggestive SNPs at $r^2 < .6$. Using these independent significant SNPs, tagged SNPs to be used in subsequent annotations were identified as all SNPs that had an MAF ≥ 0.0005 and were in LD of $r^2 \geq .6$ with at least one of the independent significant SNPs. These tagged SNPs included those from the 1000 Genomes Phase 3 reference panel and need not have been included in the GWAS performed in the current study. Genomic risk loci that were 250 kb or closer were merged into a single locus. Lead SNPs were also identified using the independent significant SNPs and were defined as those that were independent from each other at $r^2 < .1$.

Comparison to previous findings. A look-up of the independent significant and tagged SNPs for health literacy in the current study was performed in previous GWAS of general cognitive ability (Davies et al., 2018) and years of schooling (Okbay et al., 2016). We identified whether significant SNPs and tagged SNPs reported here reached either genome-wide ($p < 5 \times 10^{-8}$) or suggestive ($p < 1 \times 10^{-5}$) significance in these previous GWAS.

Gene-based analysis implemented in FUMA. Gene-based association analyses were conducted using MAGMA (Multi-marker Analysis of GenoMic Annotation; de Leeuw et al., 2015). The test carried out using MAGMA, as implemented in FUMA, was the default SNP-wise test using the mean χ^2 statistic derived on a per gene basis. SNPs were mapped to genes based on genomic location. All SNPs that were located within the gene body were used to derive a p-value describing the association found with health literacy. The SNP-wise model from MAGMA was used and the NCBI build 37 was used to determine the location and boundaries of 18,199 autosomal genes. LD within and between each gene was gauged using the 1000 genomes Phase 3 release. A Bonferroni correction was applied to control for multiple testing across 18,199 genes; the genome-wide significance threshold was $p < 2.75 \times 10^{-6}$.

Functional annotation implemented in FUMA. The independent significant SNPs and those in LD with the independent significant SNPs were annotated for functional consequences on gene functions using ANNOVAR (Wang et al., 2010) and the Ensembl genes build 85. Functionally annotated SNPs were then mapped to genes based on physical position on the genome and chromatin interaction mapping (all tissues). Intergenic SNPs were mapped to the two closest up- and downstream genes, which can result in their being assigned to multiple genes.

Gene-set analysis implemented in FUMA. In order to test whether the polygenic signal measured in the GWAS clustered in specific biological pathways, a competitive gene-set analysis was performed. Gene-set analysis was conducted in MAGMA (de Leeuw et al., 2015) using competitive testing, which examines whether genes within the gene-set are more strongly associated with health literacy than other genes. A total of 10,675 gene-sets, sourced from Gene Ontology (Ashburner et al., 2000), Reactome (Fabregat et al., 2016) and SigDB (Subramanian et al., 2005) were examined for enrichment of health literacy. A Bonferroni correction ($p < .05/10{,}675 = 4.68 \times 10^{-6}$) was applied to control for the multiple tests performed.

Gene-property analysis implemented in FUMA. A gene-property analysis was conducted using MAGMA in order to indicate the role of particular tissue types that influence differences in health literacy. The goal of this analysis was to test if, in 30 broad tissue types and 53 specific tissues, tissue-specific differential expression levels were predictive of the association of a gene with health literacy. Tissue types were taken from the GTEx v6 RNA-seq database (Ardlie et al., 2015) with expression values being log2 transformed with a pseudocount of 1 after winsorising at 50, with the average expression value being taken from each tissue. Multiple testing was controlled for using a Bonferroni correction ($p < .05/53 = 9.43 \times 10^{-4}$).

Estimation of SNP-based heritability. The proportion of variance explained by all common SNPs was estimated using univariate genome-wide complex trait analysis (GCTA-GREML; Yang et al., 2010). The sample size for the GCTA-GREML is slightly smaller than that used in the association analysis ($n = 5661$), because one individual was excluded from any pair of individuals who had an estimated coefficient of relatedness of >.025 to ensure that effects due to shared environment were not included. The same covariates were included in the GCTA-GREML as for the SNP-based association analysis.

Polygenic profile analyses. Polygenic profile scores were created using PRSice version 2 (Euesden et al., 2015; https://github.com/choishingwan/PRSice). First, we used the GWAS results for health literacy to create health literacy polygenic profile scores in an independent sample and used these scores to predict health literacy, cognitive function and educational attainment phenotypes. Polygenic profile scores for health literacy were created in 1005 genotyped participants from the Lothian Birth Cohort 1936 (LBC1936) study (Deary et al., 2007) by calculating the sum of alleles associated with health literacy across many genetic loci, weighted by the effect size for each loci. Before the polygenic scores were created, SNPs with a MAF of < 0.01 were removed and clumping was used to obtain SNPs in LD ($r^2 < .25$ within a 250 kb window). Five scores were then created that included SNPs according to the significance of the association with health literacy, based on the following p-value thresholds: $p < .01$, $p < .05$, $p < 0.1$, $p < .5$ and all SNPs. Linear regression was used to investigate whether polygenic profiles for health literacy were associated with performance on the Newest Vital Sign (Weiss et al., 2005), a test of health literacy similar in content to the ELSA health literacy test, a measure of general cognitive ability and years of schooling (see Supplementary Methods for more detail on these phenotypes). Models were adjusted for age, sex and four genetic principal components, and standardized betas were calculated.

Next, we used summary GWAS results from 21 GWAS of cognitive and health-related phenotypes to create polygenic profile scores for cognitive and health-related traits in ELSA participants. As the creation of polygenic scores requires summary GWAS results from an independent sample, the GWAS of general cognitive ability (Davies et al., 2018) was rerun removing ELSA participants. SNPs with a MAF of $< .01$ were removed and clumping was used to obtain SNPs in LD ($r^2 < .25$ within a 250 kb window) prior to the creation of the polygenic scores. Five scores were created for each phenotype based on the p-value thresholds detailed above. For Alzheimer's disease, we created a second set of scores with a 500 kb region around

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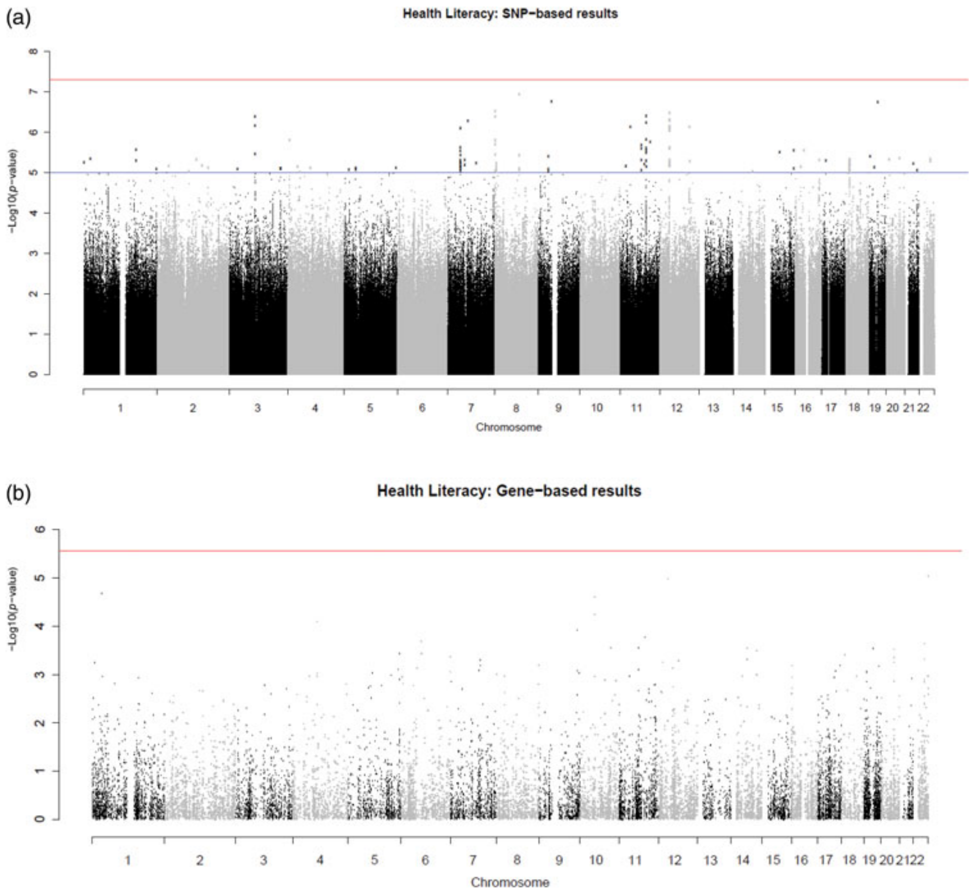

Fig. 1. (Color online) SNP-based (a) and gene-based (b) association results for health literacy. The red line indicates the threshold for genome-wide significance: $p < 5 \times 10^{-8}$ for (a), $p < 2.75 \times 10^{-6}$ for (b); the blue line in (a) indicates the threshold for suggestive significance: $p < 1 \times 10^{-5}$.

the *APOE* locus removed [hereafter called 'Alzheimer's disease (500 kb)'] to create a polygenic risk score of Alzheimer's disease with and without the *APOE* locus.

These polygenic scores were converted to *z* scores. Logistic regression was used to investigate whether polygenic profiles for cognitive and health-related traits were associated with having adequate, compared to limited, health literacy in ELSA participants. All models were adjusted for age at wave 2, sex and the 15 genetic principal components to control for population stratification. For each phenotype, five logistic regression models were run using the five polygenic scores created based on the *p*-value thresholds; thus, a total of (5 × 21) 105 models were run. To control for multiple testing, the reported *p*-values are false discovery rate-corrected. This method controls for the number of false positive results in those that reach significance (Benjamini & Hochberg, 1995). A multivariate logistic regression model was run including all of the significant polygenic scores, controlling for age, sex and 15 genetic principal components to test whether these polygenic scores independently contributed to health literacy.

Results

Of the 7358 participants who remained following genotyping quality control procedures, 5783 (3160 female; 54.6%) had completed the health literacy test at wave 2 and form the analytic sample (mean age = 65.49, *SD* = 9.55). A total of 4012 (69.4%) participants had adequate health literacy, whereas 1771 (30.6%) participants had limited health literacy. Participants with limited health literacy were older (mean age = 67.76, *SD* = 10.00) than participants with adequate health literacy (mean age = 64.72, *SD* = 9.19; $t(3140.90) = 10.91$, $p < .001$).

Genome-wide association study. A genome-wide association analysis of health literacy found no genome-wide significant ($p < 5 \times 10^{-8}$) SNP associations. There were 131 suggestive SNP associations ($p < 1 \times 10^{-5}$). The SNP-based Manhattan plot is shown in Figure 1 (the SNP-based QQ plot is shown in Supplementary Figure S1; suggestive SNPs are reported in Supplementary Data S1). Genomic risk loci characterization performed using FUMA with the genome-wide suggestive significance threshold ($p < 1 \times 10^{-5}$) identified 39 'independent' significant SNPs distributed within 36 loci; see Methods section for the description of independent SNP selection criteria. For consistency, we use the term 'independent suggestively significant SNP' here according to the definition that is used in the relevant analysis package and the significance threshold described above. Details of functional annotation of these independent suggestively significant SNPs and tagged SNPs within the 36 loci can be found in Supplementary Data S2.

Comparison with previous findings. Of the 39 independent suggestively significant and 253 tagged SNPs (those in LD with the independent suggestively significant SNPs), none had been reported as reaching genome-wide ($p < 5 \times 10^{-8}$) or suggestive ($p < 1 \times 10^{-5}$) significance in previous GWAS of general cognitive ability or years of education.

Gene-based analyses. No genome-wide significant findings were found from the gene-based association analysis; the gene-based association results are shown in Supplementary Data S3 (the gene-based Manhattan plot is shown in Figure 1; the QQ plot is shown in Supplementary Figure S1). The gene-set and gene-

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property analyses also did not identify any significant results (Supplementary Data S4 and S5).

SNP-based heritability. We estimated the proportion of variance explained by all common SNPs to be 0.085 ($SE = 0.072$). We note that, with the large standard error, this does not rule out zero SNP-based heritability.

We did not calculate genetic correlations between health literacy and those phenotypes included in the polygenic profile analyses as we did not have adequate power in this sample to utilize either the LD score regression method or, for those phenotypes also available in ELSA, bivariate GCTA-GREML. The mean chi-squared value for the health literacy phenotype was 1.009, which is below the LD score regression recommended threshold of 1.02 (Bulik-Sullivan et al., 2015). This indicates that there is too small a polygenic signal for these methods to work with.

Health literacy polygenic profile scores predicting health literacy, cognitive function and educational attainment in LBC1936. Polygenic profile score for health literacy did not significantly predict performance on the Newest Vital Sign, cognitive ability or years of schooling in LBC1936 (Supplementary Table S2).

Cognitive and health-related polygenic scores predicting health literacy in ELSA. Table 1 shows the results of the association between cognitive and health-related polygenic scores and health literacy in ELSA participants, using the most predictive threshold. Supplementary Table S3 reports the full results for all thresholds.

Increased odds of having adequate, compared to limited, health literacy were associated with a one standard deviation higher polygenic profile score for general cognitive ability [$OR = 1.34$, 95% CI (1.26, 1.42)], verbal-numerical reasoning [OR = 1.30, 95% CI (1.23 -1.39)] and years of schooling [OR = 1.29, 95% CI (1.21, 1.36)]. Reaction time and childhood IQ polygenic scores did not predict health literacy. Decreased odds of having adequate health literacy were associated with a 1 standard deviation higher polygenic profile score for poorer self-rated health [$OR = 0.92$, 95% CI (0.87, 0.98)] and schizophrenia [$OR = 0.91$, 95% CI (0.85, 0.96)]. No other polygenic scores predicted health literacy.

To examine whether each polygenic profile score improved the prediction of health literacy, the Nagelkerke pseudo R^2 value for a model with only the covariates (age, sex and 15 genetic principal components) was subtracted from the Nagelkerke pseudo R^2 for the model with both covariates and the polygenic score (Table 1). Polygenic profile scores for general cognitive ability, verbal-numerical reasoning and years of schooling accounted for 2.2%, 1.8% and 1.7%, respectively, of the variance in health literacy. The variance in health literacy accounted for by the self-reported health and schizophrenia polygenic scores was small, at 0.2% and 0.3%, respectively.

Table 2 shows the results of the multivariate logistic regression in which polygenic scores for general cognitive ability, verbal-numerical reasoning, years of schooling, self-rated health and schizophrenia were all entered simultaneously. The odds ratios for all polygenic scores were attenuated in this model. Increased odds of having adequate, compared to limited, health literacy were significantly associated with the following: higher polygenic scores for general cognitive ability [$OR = 1.18$, 95% CI (1.06, 1.32)] and years of schooling [$OR = 1.19$, 95% CI (1.11, 1.27)]; and lower polygenic risk for schizophrenia [$OR = 0.93$, 95% (CI 0.88, 0.99)]. Together, these polygenic profile scores accounted for 3.0% of the variance in health literacy. In this multivariate model, the association between the verbal-numerical reasoning polygenic profile score and health literacy was attenuated and nonsignificant. This is not surprising as the general cognitive ability polygenic score is derived from a metaanalysis, which includes the verbal-numerical reasoning test (Davies et al., 2018). The self-rated health polygenic score was also attenuated and nonsignificant in this model.

Discussion

Using a sample of 5783 middle-aged and older adults living in England, no SNPs were found to be significantly associated with health literacy; however, we report 131 suggestive SNP associations within 36 independent genomic loci. Using polygenic profile scoring, this study found that genetic variants previously associated with higher general cognitive ability, verbal-numerical reasoning and more years of schooling were associated with having adequate health literacy, whereas genetic variants previously found to be associated with poorer self-rated health and a diagnosis of schizophrenia were associated with having limited health literacy. These results suggest that the phenotypic associations frequently reported between health literacy and cognitive function, and health literacy and health might be partly due to shared genetic etiology. In a multivariate model in which all the significant polygenic scores were entered simultaneously, higher polygenic scores for general cognitive ability, years of schooling and schizophrenia remained significant, suggesting these polygenic scores independently contribute to performance on a health literacy test.

A number of studies have reported phenotypic associations between performance on tests of health literacy and cognitive function (Boyle et al., 2013; Mõttus et al., 2014; Murray et al., 2011; Reeve & Basalik, 2014). Due to the strength of these reported associations, some researchers (Mõttus et al., 2014; Reeve & Basalik, 2014) have proposed that health literacy and cognitive function are not separate constructs and are instead assessing to a substantial extent the same underlying ability. To investigate this overlap, Reeve and Basalik (2014) entered three health literacy tests and six cognitive tests into an exploratory factor analysis. No unique health literacy factor emerged, and in fact, the three health literacy tests each loaded on different factors (Reeve & Basalik, 2014). The authors concluded that there is very little evidence that health literacy is unique from cognitive function (Reeve & Basalik, 2014). The current study found that the genetic variants associated with cognitive function make significant contributions to performance on tests of health literacy, providing additional evidence that health literacy and cognitive function are intrinsically related and that they might, in part, be associated with the same underlying construct.

Some researchers have suggested that educational attainment can be used as a proxy for cognitive ability in genetic studies (Hill, Marioni et al., 2019; Okbay et al., 2016) because: (a) there are large phenotypic and genetic correlations between cognitive function and educational attainment (Hagenaars et al., 2016) and (b) it is much easier to collect information on educational attainment than it is to administer cognitive assessments in large studies. In the current study, when all significant polygenic scores were entered simultaneously, the general cognitive ability polygenic score and the years of schooling polygenic score both had independent associations with health literacy. Thus, at least when measuring health literacy, it might not be appropriate to consider cognitive function and educational attainment

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Table 1. Association between polygenic profiles of cognitive, socioeconomic, health and personality traits with having adequate health literacy, controlling for age, sex and 15 genetic principal components

	Threshold	*OR*	95% CI		R^{2*}	*p*-value†
			Lower	Upper		
Cognitive traits and proxies						
General cognitive ability	1	1.339	1.261	1.422	.0219	**3.67×10^{-15}**
Verbal-numerical reasoning	0.5	1.304	1.228	1.385	.0179	**3.67×10^{-15}**
Reaction time	0.5	0.954	0.902	1.010	.0006	.2504
Childhood IQ	1	1.061	1.001	1.123	.0010	.1281
Years of schooling	0.1	1.285	1.212	1.362	.0171	**3.67×10^{-15}**
Socioeconomic measures						
Social deprivation	0.01	0.970	0.916	1.028	.0003	.4530
General health measures						
Self-rated health	0.1	0.923	0.871	0.977	.0018	**.0359**
FEV1	1	0.932	0.879	0.988	.0013	.0880
Longevity	0.05	0.970	0.915	1.029	.0002	.4530
Gait speed	1	1.003	0.946	1.064	.0000	.9720
BMI	0.5	0.942	0.889	0.998	.0010	.1281
Waist-to-hip ratio	0.5	0.968	0.913	1.025	.0003	.4417
Chronic diseases						
Type 2 diabetes	0.05	1.043	0.984	1.105	.0005	.3217
High blood pressure	0.1	1.056	0.997	1.118	.0008	.1648
Health behaviours						
Smoking status	0.5	0.941	0.888	0.996	.0011	.1200
Alcohol consumption	0.5	0.940	0.880	1.004	.0008	.1648
Neuropsychiatric disorders						
Alzheimer's disease	0.1	1.044	0.986	1.105	.0005	.3080
Alzheimer's disease (500 kb)	0.1	1.043	0.985	1.104	.0005	.3217
Major depressive disorder	0.05	0.936	0.884	0.992	.0012	.1104
Schizophrenia	1	0.905	0.853	0.960	.0026	**.0062**
Personality traits						
Neuroticism	0.1	0.927	0.875	0.983	.0015	.0602
Conscientiousness	0.05	1.038	0.980	1.099	.0004	.3945

Note: FEV1 = forced expiratory volume in 1 s; BMI = body mass index. The associations between the polygenic profile with the largest effect size (threshold) and the health literacy phenotype are reported.
*Nagelkerke Pseudo R^2. R^2 is calculated by subtracting the value of a model containing only the covariates (age, sex and 15 genetic principal components) from the model including the polygenic profile score and covariates.
†*p*-values reported have been FDR-adjusted. FDR-adjusted significant *p*-values are shown in bold.

polygenic scores as proxies for the same underlying ability. On the other hand, it is possible that educational attainment was indexing some aspects of cognitive function not tapped by the phenotypes that went into the cognitive GWAS, which tended to be more fluid in characterization.

The results of the current study provide some evidence that the frequently reported associations between health literacy and health (Berkman et al., 2011) might be partly due to shared genetic influences. We found that genetic variants associated with poorer self-reported health and having a diagnosis of schizophrenia were associated with having poorer health literacy. Many studies have reported phenotypic associations between health literacy and self-reported health status (Berkman et al., 2011; von Wagner et al., 2007; Wolf et al., 2005). There has been relatively little research investigating health literacy and schizophrenia; however, health literacy has been found to be negatively associated with other mental health outcomes including mental health status (Wolf et al., 2005) and depressive symptoms (Gazmararian et al., 2000). The ELSA sample used here consisted of relatively healthy community-dwelling adults. In this sample of participants without schizophrenia, having a higher polygenic risk of schizophrenia was associated with poorer health literacy. This mimics the results seen for schizophrenia and cognitive function. Individuals with higher polygenic risk of schizophrenia tend to perform more poorly on tests of cognitive function (Hagenaars et al., 2016; McIntosh et al., 2013). In this study, whereas the association between polygenic risk of schizophrenia and poorer health literacy was attenuated when also controlling for cognitive polygenic scores, polygenic risk of schizophrenia remained a

Table 2. Multivariate models of the association between polygenic profiles of cognitive and health traits with having adequate health literacy, controlling for age, sex and 15 genetic principal components

		95% CI		
	OR	Lower	Upper	*p*-value*
General cognitive ability	1.182	1.058	1.320	**.0076**
Verbal-numerical reasoning	1.062	0.953	1.184	.3489
Years of schooling	1.186	1.112	1.265	**9.50×10^{-7}**
Self-rated health	0.987	0.930	1.048	.6691
Schizophrenia	0.929	0.875	0.987	**.0287**

Note: *OR*s and 95% CIs are from a model in which all five polygenic scores are entered simultaneously, controlling for age, sex and 15 genetic principal components.
**p* values reported have been FDR-adjusted (after a false discovery rate correction across five tests). FDR-adjusted significant *p*-values are shown in bold.

significant predictor of health literacy, suggesting the associations reported here are not simply because of any overlap between cognitive function and schizophrenia.

One strength of the current study is that we used GWAS summary results from a large number of cognitive and health-related traits, which enabled a comprehensive investigation of the shared genetic influences between health literacy, cognitive function and health. Whereas phenotypic associations between health literacy and health-related traits such as type 2 diabetes (Wolf et al., 2005) and Alzheimer's disease (Kaup et al., 2014; Yu et al., 2017) have been identified, we did not find that genetic variants previously associated with these health-related traits were associated with health literacy in this study. One limitation of the current study is that the quality of the polygenic profile scores created depends on the quality of the original GWAS. Many of the GWAS are metaanalyses, which introduces heterogeneity in both the genetic methods used and in measuring the phenotype. Some of the GWAS have relatively small sample sizes. It is possible that we did not find an association between some of the health and cognitive polygenic scores with health literacy because the original GWAS was underpowered to identify genetic associations with the phenotype.

Unlike recent GWAS of cognitive function (Davies et al., 2018; Savage et al., 2018), which found many genetic variants associated with cognitive function, we found no SNPs significantly associated with health literacy. It is now well known that for polygenic traits, the effect of individual genetic variants on a trait is likely to be very small and therefore larger sample sizes than the one used here are required to identify such associations (Deary et al., 2019). Identification of many genetic variants associated with cognitive function is only now possible because of the ever-increasing sample sizes. For cognitive function, early studies of approximately 3500 individuals found no significant SNPs (Davies et al., 2011). However, a more recent GWAS of cognitive function used data from over 300,000 individuals and found over 1000 significant SNPs (Davies et al., 2018). The GWAS reported here is therefore underpowered. Given the cognitive literature, much larger samples sizes — at least 10 times larger — than the sample size used here are probably needed to begin to understand the specific genetic variants involved in health literacy. There are, however, few large studies that measure health literacy. The present study is the first investigation of the molecular genetic contributions to health literacy. We encourage other groups with both health literacy and genetic data to explore the genetic associations of health literacy. In an effort to increase power, future studies should look to conduct a metaanalysis of GWAS of health literacy.

None of the suggestively significant SNPs identified in this study have previously been reported as genome-wide significantly associated with cognitive function (Davies et al., 2018) or years of schooling (Okbay et al., 2016). If health literacy, cognitive ability and education do have shared genetic influences, and the suggestive health literacy findings reported here are found to be true associations, then they appear to be associated with an aspect of health literacy that does not have shared genetic etiology with cognitive function or years of education. However, given the small sample size, some of the observed suggestive signals reported here may be due to chance.

The present study found that the SNP-based heritability for health literacy was 8.5% (*SE* = 7.2%), which is lower than has been reported in studies testing the SNP-based heritability of cognitive phenotypes (Davies et al., 2011, 2018). The heritability estimates for cognitive function were calculated using much larger samples than were used here. For example, the SNP-based heritability for general cognitive function was found to be 25% (*SE* = 0.6%) using a sample of 86,010 UK Biobank participants (Davies et al., 2018). Measurement characteristics of health literacy in the present study probably lowered the estimate of SNP-based heritability. In common with other studies using this test (Gale et al., 2015; Kobayashi et al., 2014), we dichotomized test scores into adequate (4/4 correct) and limited (<4 correct) health literacy. Given the brief nature of this test, and given that we have defined health literacy as a dichotomy, it is possible that the SNP-based heritability estimate reported here was attenuated. Longer tests, which can capture the continuum in health literacy variance, would be preferable and could test this possibility. On the other hand, we note that dichotomous variables in this general area can result in larger SNP-based heritability; for example, having or not having a college or university degree in the UK Biobank sample had a SNP-based heritability of 21% (*SE* = 0.6%; Davies et al., 2016).

One strength of this study is that health literacy was measured consistently in all participants. One limitation is that the health literacy measure used in ELSA is a brief, four-item test that has a ceiling effect. That is, 70% of participants scored full marks (4/4) on this test. Despite the brief nature of the ELSA health literacy test, and despite the ceiling effect, this measure has been found to be associated with various health outcomes, including mortality (Bostock & Steptoe, 2012). In the current study, this health literacy test was sensitive enough to identify associations with polygenic scores for cognitive and health-related traits. Future research examining the genetic contributions to health literacy should use more detailed and continuous measures of health literacy.

Phenotypic associations have consistently been found between health literacy — the skills and ability required to manage ones health — and cognitive function and health. This study is the first to investigate whether health literacy and cognitive function, and health literacy and health, share genetic architecture. In this study we investigated the genetic associations of health literacy and tested whether genetic contributions to cognitive function and health are associated with health literacy. No SNPs had genome-wide significant associations with health literacy. Polygenic scores for cognitive function, years of schooling, self-reported health and schizophrenia were significantly associated with performance on a brief test of health literacy. These results indicate that the phenotypic associations between health literacy and cognitive function, and health literacy and health may be partly due to shared genetic etiology between these traits. Future studies should build on the heritability estimate and polygenic profile results reported here and explore the genetic overlap and distinctiveness of health literacy, cognitive ability, education

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and health. As the number of participants increases, we will be able to determine the SNPs, genes, and gene-sets that are shared and distinct between health literacy, cognitive function and health.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2019.28.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Altshuler, D. M., Durbin, R. M., Abecasis, G. R., Bentley, D. R., Chakravarti, A., Clark, A. G., . . . Genomes Project Consortium. (2015). A global reference for human genetic variation. *Nature*, *526*, 68–74.

Ardlie, K. G., DeLuca, D. S., Segre, A. V., Sullivan, T. J., Young, T. R., Gelfand, E. T., . . . GTEx Consortium. (2015). The Genotype-Tissue Expression (GTEx) pilot analysis: Multitissue gene regulation in humans. *Science*, *348*, 648–660.

Ashburner, M., Ball, C. A., Blake, J. A., Botstein, D., Butler, H., Cherry, J. M., . . . Gene Ontology Consortium. (2000). Gene ontology: Tool for the unification of biology. *Nature Genetics*, *25*, 25–29.

Baker, D. W. (2006). The meaning and the measure of health literacy. *Journal of General Internal Medicine*, *21*, 878–883.

Baker, D. W., Wolf, M. S., Feinglass, J., & Thompson, J. A. (2008). Health literacy, cognitive abilities, and mortality among elderly persons. *Journal of General Internal Medicine*, *23*, 723–726.

Baker, D. W., Wolf, M. S., Feinglass, J., Thompson, J. A., Gazmararian, J. A., & Huang, J. (2007). Health literacy and mortality among elderly persons. *Archives of Internal Medicine*, *167*, 1503–1509.

Batty, G. D., Deary, I. J., & Gottfredson, L. S. (2007). Premorbid (early life) IQ and later mortality risk: Systematic review. *Annals of Epidemiology*, *17*, 278–288.

Batty, G. D., Mortensen, E. L., & Osler, M. (2005). Childhood IQ in relation to later psychiatric disorder: Evidence from a Danish birth cohort study. *British Journal of Psychiatry*, *187*, 180–181.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B (Methodological)*, *57*, 289–300.

Berkman, N. D., Sheridan, S. L., Donahue, K. E., Halpern, D. J., & Crotty, K. (2011). Low health literacy and health outcomes: An updated systematic review. *Annals of Internal Medicine*, *155*, 97–107.

Bostock, S., & Steptoe, A. (2012). Association between low functional health literacy and mortality in older adults: Longitudinal cohort study. *BMJ*, *344*, e1602.

Boyle, P. A., Yu, L., Wilson, R. S., Segawa, E., Buchman, A. S., & Bennett, D. A. (2013). Cognitive decline impairs financial and health literacy among community-based older persons without dementia. *Psychology and Aging*, *28*, 614–624.

Bulik-Sullivan, B. K., Loh, P. R., Finucane, H. K., Ripke, S., Yang, J., Patterson, N., . . . Schizophrenia Working Group. (2015). LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics*, *47*, 291–295.

Calvin, C. M., Batty, G. D., Der, G., Brett, C. E., Taylor, A., Pattie, A., . . . Deary, I. J. (2017). Childhood intelligence in relation to major causes of death in 68 year follow-up: Prospective population study. *BMJ*, *357*, j2708.

Calvin, C. M., Deary, I. J., Fenton, C., Roberts, B. A., Der, G., Leckenby, N., & Batty, G. D. (2011). Intelligence in youth and all-cause-mortality: Systematic review with meta-analysis. *International Journal of Epidemiology*, *40*, 626–644.

Christensen, G. T., Mortensen, E. L., Christensen, K., & Osier, M. (2016). Intelligence in young adulthood and cause-specific mortality in the Danish Conscription Database — A cohort study of 728,160 men. *Intelligence*, *59*, 64–71.

Davies, G., Lam, M., Harris, S. E., Trampush, J. W., Luciano, M., Hill, W. D., . . . Deary, I. J. (2018). Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. *Nature Communications*, *9*, 2098.

Davies, G., Marioni, R. E., Liewald, D. C., Hill, W. D., Hagenaars, S. P., Harris, S. E., . . . Deary, I. J. (2016). Genome-wide association study of cognitive functions and educational attainment in UK Biobank ($N = 112$ 151). *Molecular Psychiatry*, *21*, 758–767.

Davies, G., Tenesa, A., Payton, A., Yang, J., Harris, S. E., Liewald, D., . . . Deary, I. J. (2011). Genome-wide association studies establish that human intelligence is highly heritable and polygenic. *Molecular Psychiatry*, *16*, 996–1005.

Deary, I. J., Gow, A. J., Taylor, M. D., Corley, J., Brett, C., Wilson, V., . . . Starr, J. M. (2007). The Lothian Birth Cohort 1936: A study to examine influences on cognitive ageing from age 11 to age 70 and beyond. *BMC Geriatrics*, *7*, 28.

Deary, I. J., Harris, S. E., & Hill, W. D. (2019). What genome-wide association studies reveal about the association between intelligence and physical health, illness, and mortality. *Current Opinion in Psychology*, *27*, 6–12.

Dickson, H., Laurens, K. R., Cullen, A. E., & Hodgins, S. (2012). Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia. *Psychological Medicine*, *42*, 743–755.

Durbin, R. (2014). Efficient haplotype matching and storage using the positional Burrows-Wheeler transform (PBWT). *Bioinformatics*, *30*, 1266–1272.

Euesden, J., Lewis, C. M., & O'Reilly, P. F. (2015). PRSice: Polygenic risk score software. *Bioinformatics*, *31*, 1466–1468.

Fabregat, A., Sidiropoulos, K., Garapati, P., Gillespie, M., Hausmann, K., Haw, R., . . . D'Eustachio, P. (2016). The reactome pathway knowledgebase. *Nucleic Acids Research*, *44*, D481–D487.

Fawns-Ritchie, C., Starr, J. M., & Deary, I. J. (2018a). Health literacy, cognitive ability and smoking: A cross-sectional analysis of the English Longitudinal Study of Ageing. *BMJ Open*, *8*, e023929.

Fawns-Ritchie, C., Starr, J. M., & Deary, I. J. (2018b). Role of cognitive ability in the association between functional health literacy and mortality in the Lothian Birth Cohort 1936: A prospective cohort study. *BMJ Open*, *8*, e022502.

Gale, C. R., Deary, I. J., Boyle, S. H., Barefoot, J., Mortensen, L. H., & Batty, D. (2008). Cognitive ability in early adulthood and risk of 5 specific psychiatric disorders in middle age: The Vietnam experience study. *Archives of General Psychiatry*, *65*, 1410–1418.

Gale, C. R., Deary, I. J., Wardle, J., Zaninotto, P., & Batty, G. D. (2015). Cognitive ability and personality as predictors of participation in a national colorectal cancer screening programme: The English Longitudinal Study of Ageing. *Journal of Epidemiology and Community Health*, *69*, 530–535.

Gale, C. R., Hatch, S. L., Batty, G. D., & Deary, I. J. (2009). Intelligence in childhood and risk of psychological distress in adulthood: The 1958 National Child Development Survey and the 1970 British Cohort Study. *Intelligence*, *37*, 592–599.

Gazmararian, J., Baker, D., Parker, R., & Blazer, D. G. (2000). A multivariate analysis of factors associated with depression: Evaluating the role of health literacy as a potential contributor. *Archives of Internal Medicine*, *160*, 3307–3314.

Hagenaars, S. P., Harris, S. E., Davies, G., Hill, W. D., Liewald, D. C. M., Ritchie, S. J., . . . Deary, I. J. (2016). Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N = 112151) and 24 GWAS consortia. *Molecular Psychiatry*, *21*, 1624–1632.

Haworth, C. M. A., Wright, M. J., Luciano, M., Martin, N. G., de Geus, E. J. C., van Beijsterveldt, C. E. M., . . . Plomin, R. (2010). The heritability of general cognitive ability increases linearly from childhood to young adulthood. *Molecular Psychiatry*, *15*, 1112–1120.

Hill, W. D., Harris, S. E., & Deary, I. J. (2019). What genome-wide association studies reveal about the association between intelligence and mental health. *Current Opinion in Psychology*, *27*, 25–30.

Hill, W. D., Marioni, R. E., Maghzian, O., Ritchie, S. J., Hagenaars, S. P., McIntosh, A. M., . . . Deary, I. J. (2019). A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence. *Molecular Psychiatry*, *24*, 169–181.

Institute of Medicine. (2004). *Health literacy: A prescription to end confusion*. Washington, DC: The National Academies Press.

Kaup, A. R., Simonsick, E. M., Harris, T. B., Satterfield, S., Metti, A. L., Ayonayon, H. N., . . . Yaffe, K. (2014). Older adults with limited literacy are at increased risk for likely dementia. *Jounrnals Gerontology. Series A Biological Sciences and Medical Sciences*, *69*, 900–906.

Knopman, D. S., Mosley, T. H., Catellier, D. J., Coker, L. H., & Atherosclerosis Risk in Communities Study Brain MRI Study. (2009). Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: The ARIC MRI study. *Alzheimers & Dementia*, *5*, 207–214.

Kobayashi, L. C., Wardle, J., & von Wagner, C. (2014). Limited health literacy is a barrier to colorectal cancer screening in England: Evidence from the English Longitudinal Study of Ageing. *Preventative Medicine*, *61*, 100–105.

de Leeuw, C. A., Mooij, J. M., Heskes, T., & Posthuma, D. (2015). MAGMA: Generalized gene-set analysis of GWAS data. *Plos Computational Biology*, *11*, e1004219.

Loh, P. R., Danecek, P., Palamara, P. F., Fuchsberger, C., Reshef, Y. A., Finucane, H. K., . . . Price, A. L. (2016). Reference-based phasing using the Haplotype Reference Consortium panel. *Nature Genetics*, *48*, 1443–1448.

McCarthy, S., Das, S., Kretzschmar, W., Delaneau, O., Wood, A. R., Teumer, A., . . . Haplotype Reference Consortium. (2016). A reference panel of 64,976 haplotypes for genotype imputation. *Nature Genetics*, *48*, 1279–1283.

McGurn, B., Deary, I. J., & Starr, J. M. (2008). Childhood cognitive ability and risk of late-onset Alzheimer and vascular dementia. *Neurology*, *71*, 1051–1056.

McIntosh, A. M., Gow, A., Luciano, M., Davies, G., Liewald, D. C., Harris, S. E., . . . Deary, I. J. (2013). Polygenic risk for schizophrenia is associated with cognitive change between childhood and old age. *Biological Psychiatry*, *73*, 938–943.

Mons, U., Schottker, B., Muller, H., Kliegel, M., & Brenner, H. (2013). History of lifetime smoking, smoking cessation and cognitive function in the elderly population. *European Journal of Epidemiology*, *28*, 823–831.

Mõttus, R., Luciano, M., Starr, J. M., & Deary, I. J. (2013). Diabetes and lifelong cognitive ability. *Journal of Psychosomatic Research*, *75*, 275–278.

Mõttus, R., Johnson, W., Murray, C., Wolf, M. S., Starr, J. M., & Deary, I. J. (2014). Towards understanding the links between health literacy and physical health. *Health Psychology*, *33*, 164–173.

Murray, C., Johnson, W., Wolf, M. S., & Deary, I. J. (2011). The association between cognitive ability across the lifespan and health literacy in old age: The Lothian Birth Cohort 1936. *Intelligence*, *39*, 178–187.

O'Conor, R., Wolf, M. S., Smith, S. G., Martynenko, M., Vicencio, D. P., Sano, M., . . . Federman, A. D. (2015). Health literacy, cognitive function, proper use, and adherence to inhaled asthma controller medications among older adults with asthma. *Chest*, *147*, 1307–1315.

Okbay, A., Beauchamp, J. P., Fontana, M. A., Lee, J. J., Pers, T. H., Rietveld, C. A., . . . Benjamin, D. J. (2016). Genome-wide association study identifies 74 loci associated with educational attainment. *Nature*, *533*, 539–542.

Pavlik, V. N., Hyman, D. J., & Doody, R. (2005). Cardiovascular risk factors and cognitive function in adults 30–59 years of age (NHANES III). *Neuroepidemiology*, *24*, 42–50.

Plomin, R., & Deary, I. J. (2015). Genetics and intelligence differences: Five special findings. *Molecular Psychiatry*, *20*, 98–108.

Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., & Sklar, P. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, *460*, 748–752.

Reeve, C. L., & Basalik, D. (2014). Is health literacy an example of construct proliferation? A conceptual and empirical evaluation of its redundancy with general cognitive ability. *Intelligence*, *44*, 93–102.

Richards, M., Jarvis, M. J., Thompson, N., & Wadsworth, M. E. J. (2003). Cigarette smoking and cognitive decline in midlife: Evidence from a prospective birth cohort study. *American Journal of Public Health*, *93*, 994–998.

Savage, J. E., Jansen, P. R., Stringer, S., Watanabe, K., Bryois, J., de Leeuw, C. A., . . . Posthuma, D. (2018). Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nature Genetics*, *50*, 912–919.

Scult, M. A., Paulli, A. R., Mazure, E. S., Moffitt, T. E., Hariri, A. R., & Strauman, T. J. (2017). The association between cognitive function and subsequent depression: A systematic review and meta-analysis. *Psychological Medicine*, *47*, 1–17.

Serper, M., Patzer, R. E., Curtis, L. M., Smith, S. G., O'Conor, R., Baker, D. W., & Wolf, M. S. (2014). Health literacy, cognitive ability, and functional health status among older adults. *Health Service Research*, *49*, 1249–1267.

Singh-Manoux, A., & Marmot, M. (2005). High blood pressure was associated with cognitive function in middle-age in the Whitehall II study. *Journal of Clinical Epidemiology*, *58*, 1308–1315.

Steptoe, A., Breeze, E., Banks, J., & Nazroo, J. (2013). Cohort profile: The English longitudinal study of ageing. *International Journal of Epidemiology*, *42*, 1640–1648.

Subramanian, A., Tamayo, P., Mootha, V. K., Mukherjee, S., Ebert, B. L., Gillette, M. A., . . . Mesirov, J. P. (2005). Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. *PNAS*, *102*, 15545–15550.

Taylor, M. D., Hart, C. L., Smith, G. D., Starr, J. M., Hole, D. J., Whalley, L. J., . . . Deary, I. J. (2003). Childhood mental ability and smoking cessation in adulthood: prospective observational study linking the Scottish Mental Survey 1932 and the Midspan studies. *Jounral of Epidemiology and Community Health*, *57*, 464–465.

Wang, K., Li, M. Y., & Hakonarson, H. (2010). ANNOVAR: Functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Research*, *38*, e164.

von Wagner, C., Knight, K., Steptoe, A., & Wardle, J. (2007). Functional health literacy and health-promoting behaviour in a national sample of British adults. *Journal of Epidemiology Community Health*, *61*, 1086–1090.

Watanabe, K., Taskesen, E., van Bochoven, A., & Posthuma, D. (2017). Functional mapping and annotation of genetic associations with FUMA. *Nature Communications*, *8*, 1826.

Weiss, B. D., Mays, M. Z., Martz, W., Castro, K. M., DeWalt, D. A., Pignone, M. P., . . . Hale, F. A. (2005). Quick assessment of literacy in primary care: The newest vital sign. *The Annals of Family Medicine*, *3*, 514–522.

Wolf, M. S., Gazmararian, J. A., & Baker, D. W. (2005). Health literacy and functional health status among older adults. *Archives of Internal Medicine*, *165*, 1946–1952.

Wraw, C., Deary, I. J., Gale, C. R., & Der, G. (2015). Intelligence in youth and health at age 50. *Intelligence*, *53*, 23–32.

Wraw, C., Der, G., Gale, C. R., & Deary, I. J. (2018). Intelligence in youth and health behaviours in middle age. *Intelligence*, *69*, 71–86.

Yang, J. A., Benyamin, B., McEvoy, B. P., Gordon, S., Henders, A. K., Nyholt, D. R., . . . Visscher, P. M. (2010). Common SNPs explain a large proportion of the heritability for human height. *Nature Genetics*, *42*, 565–569.

Yu, L., Wilson, R. S., Schneider, J. A., Bennett, D. A., & Boyle, P. A. (2017). Financial and health literacy predict incident Alzheimer's disease dementia and pathology. *Journal of Alzheimers Disease*, *56*, 1485–1493.

Zammit, S., Allebeck, P., David, A. S., Dalman, C., Hemmingsson, T., Lundberg, I., & Lewis, G. (2004). A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Archives of General Psychiatry*, *61*, 354–360.

7.3. Conclusion

The study reported in Section 7.2 found no common genetic variants (single nucleotide polymorphisms) to be significantly associated with health literacy. However, genetic variants previously associated with higher general cognitive ability, verbal-numerical reasoning, and more years of education were associated with greater odds of having adequate, compared to limited, health literacy. Genetic variants previously associated with poorer self-rated health and a diagnosis of schizophrenia were associated with reduced odds of having adequate health literacy. The results of this chapter indicate that the previously-reported phenotypic associations between health literacy, cognitive ability and health might partly be due to shared genetic influences between these traits.

Chapter 8 will provide a general overview of the empirical work presented in Chapters 4 to 7 of this thesis, and will then discuss how this new empirical research contributes to literature reviewed in Chapters 1 to 3.

8. General discussion

This thesis sought to better understand the relationship between health literacy and cognitive ability, and to investigate how these two abilities contribute to health. Specifically, the aims of this thesis were:

- **Main aim:** To investigate the unique contributions of health literacy and cognitive ability to aspects of health.
- **Secondary aim:** To investigate further the association between health literacy and cognitive ability.

8.1. Summary of findings

These aims were investigated by testing the independent associations of scores on tests of health literacy and cognitive ability with three aspects of health—smoking status, diabetes status, and mortality. Using middle-aged and older participants from the English Longitudinal Study of Ageing (ELSA), Chapter 4 investigated the association between health literacy and cognitive ability with smoking behaviour. In this cross-sectional study, two measures of smoking were investigated; whether participants reported ever smoking, and, in ever smokers, whether participants continued to smoke or had quit. When health literacy and cognitive ability were entered into the models individually, adequate (compared to limited) health literacy and higher cognitive ability were associated with being less likely to report ever smoking and, in ever smokers, being less likely to report smoking nowadays. These associations remained, though were reduced in size, when health literacy and cognitive ability were entered concurrently. After adjustment for education and occupational social class, neither health literacy nor cognitive ability were associated with reporting ever smoking. In ever smokers, participants with adequate health literacy and higher cognitive ability were more likely to have quit smoking, even after adjusting for education and social class.

Again using ELSA participants, Chapter 5 tested whether scores on tests of health literacy and cognitive ability were associated with self-reporting diabetes, and, in those who did not self-report diabetes, risk of developing diabetes over a 10 year follow-up. When health literacy and cognitive ability were examined individually, adequate health literacy and higher cognitive ability were associated with lower rates of self-reported diabetes and a lower risk of developing diabetes during follow-up. When examined concurrently, the associations were attenuated, but health literacy and cognitive ability remained significantly associated with diabetes. The relationship between health literacy, cognitive ability and cross-sectional diabetes status was attenuated and non-significant when adjusting for body mass index (BMI) and health behaviours. The associations between health literacy and cognitive ability with risk of diabetes were attenuated when adjusting for BMI and health behaviours; however, they remained significant predictors. After additionally adjusting for education and social class, the associations were further attenuated, and neither health literacy nor cognitive ability predicted diabetes risk. The results reported in Chapters 4 and 5 posit that health literacy and cognitive ability, though related, are separate constructs and they both have independent associations with health.

Using data from the Lothian Birth Cohort 1936 (LBC1936), a narrow-age sample of older Scottish adults, Chapter 6 investigated the role of prior cognitive ability measured in childhood, and fluid ability measured in older age in the association between health literacy and mortality. Higher scores on the S-TOFHLA, the Newest Vital Sign, and a measure of general health literacy, but not the REALM, were associated with a lower risk of mortality. The association between health literacy and mortality was almost unchanged when adjusting for prior cognitive ability measured in childhood. When additionally adjusting for fluid cognitive ability, neither the S-TOFHLA, nor the Newest Vital Sign, nor general health literacy predicted mortality. In contrast to Chapters 4 and 5, which found that health literacy and cognitive ability had independent associations with smoking and diabetes, the results reported in Chapter 6 suggest that the association between health literacy and mortality is not independent of fluid cognitive ability measured in older adulthood.

Chapters 4, 5, and 6 focused on the phenotypic associations of health literacy, cognitive ability and aspects of health. To investigate whether the phenotypic associations reported in this thesis and elsewhere might be because health literacy, cognitive ability, and health traits share genetic aetiology, Chapter 7 sought to examine the genetic contributions to health literacy and the genetic overlap between health literacy, cognitive ability and health. Using the ELSA sample, a genome-wide association study of health literacy was carried out. No genetic variants (single nucleotide polymorphisms) were found to be significantly associated with health literacy; however, polygenic profiles for some cognitive and health-related traits were associated with performance on the ELSA health literacy test. Higher polygenic scores for general cognitive ability, verbal-numerical reasoning, and more years of schooling were associated with having adequate compared to limited health literacy. Higher polygenic scores for poor self-rated health and a higher polygenic risk for schizophrenia were associated with higher odds of having limited health literacy. The results reported in Chapter 7 indicate that at least some of the association between health literacy, cognitive ability and health might be due to shared genetic influences.

8.2. The relationship between health literacy, cognitive ability and health

The results reported in Chapters 4 and 5 suggest that health literacy and cognitive ability both have independent associations with health. A different conclusion is drawn when interpreting the results reported in Chapter 6, which indicate that health literacy does not have associations with mortality that are independent of cognitive ability. The mixed results reported in this thesis are consistent with the mixed results reported in the literature (reported in Section 3.4). Most studies find that the size of the association between health literacy and health is attenuated when adjusting for cognitive ability (with the exception of Lamar et al., 2019). Whereas some studies have found that cognitive ability entirely attenuates the association between health literacy and health (Baker et al., 2008; Bostock & Steptoe, 2012; Kobayashi et al., 2016b; Mõttus et al., 2014), others have found that the health literacy-health association is partly attenuated by cognitive ability, but that health literacy remained significantly associated with health after adjustment for cognitive ability (Mõttus et al., 2014; O'Conor et al., 2015; Serper et al., 2014).

Similar to the studies reported in the current thesis, previous studies have examined the association of health literacy and cognitive ability with a range of different health outcomes, including health behaviours (Kobayashi et al., 2016b), medication adherence (O'Conor et al., 2015), health status (Mõttus et al., 2014; Serper et al., 2014), and mortality (Baker et al., 2008; Bostock & Steptoe, 2012). It is possible that health literacy and cognitive ability might have different patterns of association with different aspects of health; however, contrasting results have been found even when measuring the same health outcome. Whereas Baker et al. (2008) and Bostock and Steptoe (2012) found that health literacy remained an independent predictor of mortality even after adjusting for cognitive ability, the results reported in Chapter 6 found that none of the four measures of health literacy used remained associated with mortality after adjusting for fluid cognitive ability.

The different patterns of attenuation might at least be partly due to the quality of the cognitive ability measures used in these studies. The studies reported in Chapters 4 and 5 used cognitive data collected from wave 2 of ELSA. The measure of cognitive ability created using ELSA data was based on scores from only a small number of relatively brief tests thought to assess verbal declarative memory (immediate and delayed recall of 10 words), processing speed (letter cancellation), and executive function (categorical fluency). Many cognitive domains, such as reasoning and working memory—domains which are known to load highly on *g* (Salthouse, 2004)—were not captured by this measure of cognitive ability. Therefore, the measure of cognitive ability used in Chapters 4 and 5 does not comprehensively assess general cognitive ability. In addition, the ELSA cognitive assessment was not administered under standardised conditions, in a laboratory setting. Instead, it was administered in the participant's own home by interviewers who were not experts in cognitive testing (Steptoe et al., 2013). This could make the cognitive test scores more prone to error. Given the strong correlations found between health literacy and cognitive ability, and given that cognitive ability was not measured comprehensively in Chapters 4 and 5, it is possible that health literacy remained significantly associated with smoking status and diabetes due to residual confounding. That is, some of the of the apparently independent contribution of health literacy on health reported in Chapters 4 and 5 could be residual cognitive capability which is not being picked up by the relatively brief measure of cognitive ability used in these studies.

In contrast to the brief (approximately 10-15 minute) cognitive assessment administered in ELSA, the cognitive assessment administered in the LBC1936 was extensive. During an approximately 1.5 to 2 hour cognitive assessment, a broad range of different cognitive domains were assessed using well-validated neuropsychological tests—many from the Wechsler Adult Intelligence Scale III (WAIS-III)—that were administered under standardised conditions by trained testers (Deary, Gow, et al., 2007; Deary et al., 2012). In Chapter 6, scores from six WAIS-III tests that assessed non-verbal reasoning (Matrix Reasoning), visuospatial ability (Block Design), working memory (Letter-Number Sequencing and Digit Span Backwards), and processing speed (Symbol Search and Digit Symbol-Coding) were used to create a composite measure of fluid ability. When adjusting for this more detailed measure of cognitive ability, health literacy—which was measured using the S-TOFHLA, the REALM and the Newest Vital Sign, as well as a general measure of health literacy—did not have associations with mortality that were independent of cognitive ability.

Taking a closer look at the cognitive ability tests used in other studies investigating the association of health literacy, cognitive ability and health provides additional evidence that part of the reason some studies have found that health literacy is independently associated with health when adjusting for cognitive ability could be due to residual confounding. Although there are some exceptions (Lamar et al., 2019; Mõttus et al., 2014), studies where health literacy was found to have associations with health that were independent of cognitive ability have tended to use relatively crude measures of global cognitive function such as the Mini-Mental Status Examination (Baker et al., 2008) or the few, quite brief ELSA cognitive tests (Bostock & Steptoe, 2012; Kobayashi et al., 2016b). More detailed cognitive ability measures, which were created by combining scores on a number of standardised tests, have tended to be used in studies that have found that health literacy was no longer associated with health after adjusting for cognitive ability (O'Conor et al., 2015; Serper et al., 2014). For example, Serper et al. (2014) found that a composite measure of fluid ability created using tests of processing speed, working memory, reasoning, long-term memory, and prospective memory, attenuated all associations of the TOFHLA, Newest Vital Sign and REALM with physical health, depression and anxiety. After adjusting for fluid ability, all significant associations between health literacy and the three health measures were attenuated and non-significant (Serper et al., 2014).

Given the limitations of the cognitive ability measures used in Chapters 4 and 5, it is difficult to conclude that health literacy and cognitive ability are both independent contributors to health. This thesis (and other research) has found some support that health literacy and cognitive ability may both make unique contributions to health. This would suggest that the health-related skills required to obtain, process and understand health information are related to, but distinct from, the general mental capabilities to reason, plan, and solve problems, and that health literacy and cognitive ability are independently associated with at least some aspects of health (e.g., smoking and diabetes status). On the other hand, if health literacy remained associated with health in these studies only because of residual cognitive capability not being captured by the relatively brief measure of cognitive ability used, then this would suggest that tests of health literacy are measuring the same underlying ability as tests of cognitive ability, as proposed by Reeve and Basalik (2014). Section 8.3 will discuss whether health literacy and cognitive ability are entirely overlapping constructs.

8.2.1. Shared genetic influences between health literacy, cognitive ability and health

To complement Chapters 4, 5, and 6, which examined the phenotypic association of health literacy, cognitive ability and health, Chapter 7 investigated the genetic associations of these traits. Genetic techniques were used to examine whether the phenotypic associations reported in this thesis and elsewhere of health literacy, cognitive ability and health might be due to shared genetic influences. This is the first report to attempt to detail the molecular genetic contributions to health literacy. The results reported in Chapter 7 found evidence that polygenic profiles for some cognitive and health-related traits were associated with performance on the ELSA health literacy test. Having more of the genetic variants previously associated with higher general cognitive ability, higher scores on a test of verbal-numerical reasoning, and more years of schooling were associated with having adequate health literacy. These results indicated that health literacy shares some genetic influences with cognitive ability. Polygenic profiles for general cognitive ability, verbal-numerical reasoning and years of schooling accounted for 2.2%, 1.8% and 1.7%, respectively, of the variance in performance on the ELSA health literacy test. Although this may sound low, it is comparable with the variance accounted for by polygenic profiles for cognitive ability predicting cognitive test scores (Hagenaars et al., 2016). And, from experience with other traits, the percentage of variance predicted by polygenic scores increases as the sample on which the original GWAS is conducted increases. For a GWAS of a complex trait, the present sample was relatively small.

Associations between polygenic profiles for some health-related traits and scores on the ELSA health literacy test were also identified. Having more of the genetic variants associated with poor self-rated health and schizophrenia were associated with lower odds of having adequate health literacy. Although, the variance in health literacy test scores accounted for by the health-related polygenic scores (0.2% for self-reported health and 0.3% for schizophrenia) was lower than that seen for cognitive ability polygenic scores, these results suggest that health literacy, self-reported health and schizophrenia may share genetic aetiology.

In a multivariate model adjusting for all significant polygenic profiles (general cognitive ability, verbal-numerical reasoning, years of schooling, self-rated health, and schizophrenia), greater odds of having adequate health literacy was associated with higher polygenic scores for general cognitive ability, years of schooling, and lower polygenic risk for schizophrenia. These polygenic scores accounted for 3% of the variance in health literacy. The polygenic associations found in the current thesis mimic those found between performance on tests of cognitive ability and polygenic profiles for cognitive and health-related traits reported elsewhere (Hagenaars et al., 2016). Although this genetic study did not determine whether health literacy and cognitive ability have independent associations with health, it provides a new line of evidence that scores on tests of health literacy and cognitive ability, and health outcomes are in part genetically related.

8.2.2. Attenuation

The relationship between health literacy and cognitive ability with health was often attenuated when additionally adjusting for other measures of health and socioeconomic status (e.g., educational attainment and occupational social class). On many occasions, the reported associations between health literacy and cognitive ability with health were no longer significant after adjustment for these measures.

This section will discuss how health behaviours and socioeconomic status attenuated the associations between health literacy and cognitive ability with health.

8.2.2.1. Health behaviours

Chapter 5 examined the association between health literacy, cognitive ability and diabetes status. Obesity is one of the largest risk factors for developing diabetes (Hussain et al., 2007). Chapter 5 investigated whether health literacy and cognitive ability were associated with diabetes independent of obesity and other unhealthy behaviours. Adjusting for BMI, current smoking status, frequency of alcohol consumption, and physical activity greatly attenuated and nullified the association between health literacy and cognitive ability with self-reporting diabetes at baseline. These same covariates also attenuated the association between health literacy and cognitive ability with risk of diabetes; however, both health literacy and cognitive ability had independent associations with diabetes risk following adjustment for health behaviours.

Health behaviours, therefore, might mediate the association of health literacy and cognitive ability with health. Those with higher health literacy and cognitive ability might tend to be equipped with the skills and abilities required to be able to understand and act upon health advice, and might be more likely to take part in health promoting behaviours which reduce the risk of morbidity (including diabetes) and mortality. This is in line with theories linking health literacy to health, which assume that health literacy has indirect associations with health through actions to promote good health and prevent disease (von Wagner et al., 2009). In their model of the pathways between health literacy and health outcomes, Paasche-Orlow and Wolf (2007) suggested that health literacy is not directly associated with health outcomes, but instead health literacy works through three types of health actions, one of which is self-care. Those with higher health literacy may have more knowledge of their disease and health in general, and therefore are better able to manage their health (Paasche-Orlow & Wolf, 2007).

Similarly, theories linking cognitive ability to health have suggested that higher cognitive ability may be associated with good health because higher cognitive ability may lead to better health self-management throughout life (Batty, Deary, & Gottfredson, 2007; Deary, Weiss, et al., 2010; Gottfredson, 2004; Gottfredson & Deary, 2004). Preventing and managing disease is a complex task that places demands on knowledge, problem solving and decision making skills (Gottfredson, 2004). Individuals with lower cognitive ability might tend not to have cognitive capabilities to look after their health and to understand and follow health advice, and this in turn could lead to poorer health.

8.2.2.2. Socioeconomic status

Education and social class are associated with both health literacy and cognitive ability (Gottfredson, 2004; Nielsen-Bohlman et al., 2004). To determine whether health literacy and cognitive ability had associations with health that were independent of education and social class the studies reported in Chapters 4 to 6 included models adjusting for these variables. Including measures of education and social class tended to attenuate the reported associations between health literacy and health, and between cognitive ability and health. Often, after adjusting for indicators of socioeconomic status, previously significant associations between health literacy and cognitive ability with health became non-significant. In Chapter 4, health literacy and cognitive ability were no longer associated with ever smoking when adjusting for age of leaving full-time education and social class. More years of education and a higher social class had relatively strong associations with reduced odds of reporting ever smoking. Similarly, in Chapter 5, the associations between health literacy and cognitive ability with diabetes were attenuated and nullified when accounting for these socioeconomic indicators. More years of education, which was associated with a lower risk of diabetes, was the main driver of this attenuation. On the other hand, some associations between health literacy and cognitive ability with health, though attenuated, survived adjustments for socioeconomic indicators. In Chapter 4, adequate health literacy and higher cognitive ability remained associated with being more likely to have quit smoking, and, in Chapter 6, higher fluid ability remained a significant predictor of mortality.

Higher childhood cognitive ability has been found to predict educational success and social class (Deary, Strand, et al., 2007; Gottfredson, 2004; Strenze, 2007). Education and occupational social class, therefore, might act as mediating variables between cognitive ability and health. Higher cognitive ability—the general ability to learn, reason and solve problems—might tend to equip individuals with the mental capabilities required to obtain higher levels of education, knowledge and skills (this might include higher health-related knowledge and skills, i.e., health literacy), and, subsequently, a higher social class (Deary, Weiss, et al., 2010). A higher level of education and/or a higher social class could lead to better health through, for example, being more knowledgeable about health, or by obtaining a safer environment obtained by a higher social class (Deary, Weiss, et al., 2010).

It is important to note that, whereas this thesis was interested in investigating whether health literacy and cognitive ability had associations with health that were independent of other health and socioeconomic measures, it did not formally test whether health behaviours and socioeconomic measures were mediating variables in associations of health literacy and cognitive ability with health. To better understand the pathways between health literacy, cognitive ability and health, studies that formally test the mediating role of health behaviours and socioeconomic status in the association between health literacy, cognitive ability and health are needed.

8.3. Health literacy as a component of cognitive ability

A second aim of this thesis was to further investigate the overlap between health literacy and cognitive ability. Health literacy and cognitive ability are strongly related. Not only do health literacy and cognitive ability have phenotypic associations, as reported in Chapters 4 to 6, they share genetic influences as well (Chapter 7). It is less clear whether health literacy and cognitive ability are separate, though related, constructs, or whether they are entirely overlapping constructs. In a study examining the overlap between health literacy and cognitive ability, Reeve and Basalik (2014) said “it is imperative to demonstrate the uniqueness of a construct by either its complete or partial independence from other comparable constructs” (Reeve & Basalik, 2014). It has been proposed that health literacy is general cognitive ability (*g*) manifested in a health-related context (Gottfredson, 2004; Reeve & Basalik, 2014). If health literacy is in fact measuring *g*, one would expect to find that adjusting for cognitive ability would substantially attenuate and nullify the association between health literacy and health.

This thesis found that adjusting for cognitive ability at least partly attenuated the association between health literacy and health. Whereas health literacy remained significantly associated with smoking status and diabetes status after adjusting for cognitive ability in Chapters 4 and 5, fluid ability entirely attenuated the association between health literacy and mortality in Chapter 6. As detailed in Section 8.1, some of the independent contribution of health literacy reported in Chapters 4 and 5 may be due to residual cognitive capability not captured by the brief measure of cognitive ability used in these chapters. Considering the results reported in this thesis, I suggest that there are at least two alternative possibilities for the relationship between health literacy and cognitive ability; these relationships are depicted in Figures 8.1 and 8.2. The first possibility is that health literacy and cognitive ability are entirely overlapping constructs (Figure 8.1), as proposed by Reeve and Basalik (2014). The second possibility is that health literacy and cognitive ability are overlapping, but partly separate constructs. That is, health literacy and cognitive ability constructs partly overlap, and are partly independent (Figure 8.2). These conceptualisations, which are described in more detail below, make the distinction between the constructs of health literacy and cognitive ability and how health literacy and cognitive ability were actually measured in the studies reported in this thesis.

8.3.1. Health literacy and cognitive ability as entirely overlapping constructs

If we assume that health literacy and cognitive ability are entirely overlapping constructs (Figure 8.1), how do we account for the findings reported in Chapters 4 and 5 where health literacy and cognitive ability both had independent associations with health? The tests of health literacy and cognitive ability used in Chapters 4 and 5 are relatively brief. It is possible that both health literacy and cognitive ability had independent associations with health because the health literacy and cognitive ability tests used in these studies did not comprehensively assess all aspects of this overall construct. The health literacy measure (green in Figure 8.2) and the cognitive ability measure (blue in Figure 8.1), though assessing partly overlapping abilities, may also be partly assessing separate parts of this overall health literacy/cognitive ability construct.

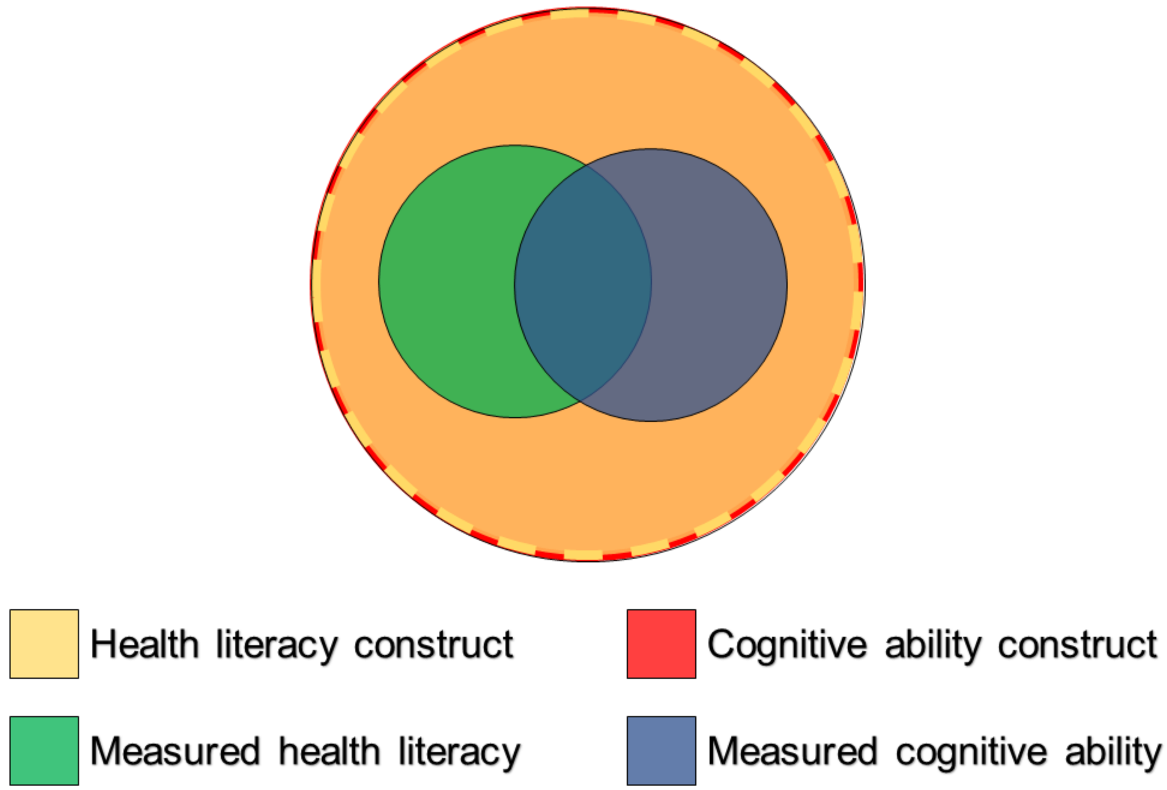


Figure 8.1. Venn diagram of the possible relationship between health literacy (yellow) and cognitive ability (red) constructs and the measures used to assess health literacy (green) and cognitive ability (blue). Health literacy and cognitive ability are conceptualised as entirely overlapping constructs.

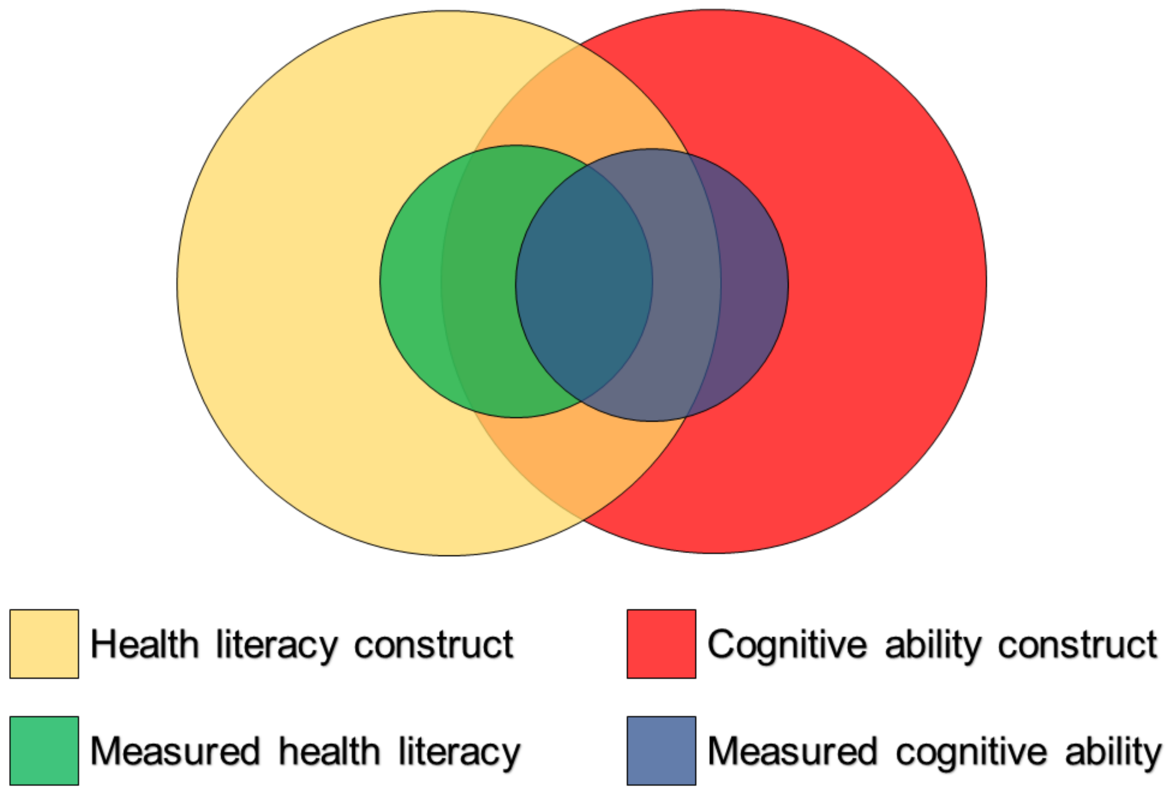


Figure 8.2. Venn diagram of the possible relationship between health literacy (yellow) and cognitive ability (red) constructs and the measures used to assess health literacy (green) and cognitive ability (blue). Health literacy and cognitive ability are conceptualised as partly overlapping and partly independent constructs.

Chapter 6 used a more detailed measure of cognitive ability and found that cognitive ability entirely attenuated the association between health literacy and mortality. This more detailed measure of cognitive ability is likely a more accurate representation of the construct of cognitive ability, therefore the blue circle in Figure 8.1 would be much larger and closer in size to the red circle representing the cognitive ability construct. This more detailed measure of cognitive ability would entirely overlap with the abilities assessed by the test of health literacy (green in Figure 8.1) and therefore health literacy would not have associations with health independent of cognitive ability, as was found in Chapter 6.

The evidence reported in this thesis is consistent with the conclusion that health literacy and cognitive ability are likely to be entirely overlapping constructs. This conclusion is based on the following: 1) the results reported in Chapters 4 and 5—that both health literacy and cognitive ability had independent associations with health—could be because the health literacy tests were measuring residual cognitive capability not being captured by the brief cognitive tests used in these studies; 2) when using more detailed tests of both health literacy and cognitive ability, Chapter 6 found that association between health literacy and mortality was entirely attenuated when adjusting for cognitive ability; and 3) Chapter 7 found evidence that health literacy and cognitive ability share genetic underpinnings, providing additional support that tests of health literacy and cognitive ability are assessing the same underlying construct.

Although the evidence reported in this thesis is most consistent with the conclusion that health literacy and cognitive ability are entirely overlapping constructs, it is important to consider other alternative explanations for the results found in this thesis. The next section will consider whether the findings of this thesis are consistent with the possibility of health literacy and cognitive ability being related, but separate constructs.

8.3.2. Health literacy and cognitive ability as separate (but related) constructs

Health literacy and cognitive ability could be separate, but related, constructs, as depicted in Figure 8.2. Theories of health literacy acknowledge that some aspects of cognitive ability (e.g., memory, information processing, and knowledge) are necessary prerequisites to health literacy (Baker, 2006; Paasche-Orlow et al., 2005; Sørensen et al., 2012). Cognitive capabilities may be necessary for adequate health literacy, but they are unlikely to be the only skills and abilities involved. Therefore the moderate-to-strong correlations reported between health literacy and cognitive ability does not rule out the possibility that these two sets of capabilities are separable, but also related.

Just as the cognitive ability tests used in this thesis have limitations, so too do the health literacy measures. These limitations must be acknowledged when trying to understand the relationship between health literacy, cognitive ability and health. Three of the empirical chapters in this thesis used a brief (less than 5 minute), four-item test of health-related reading comprehension administered in ELSA. The ELSA sample consisted of relatively healthy, community-dwelling middle-aged and older adults. These participants found this health literacy test relatively easy. Most ELSA participants (70%) scored full marks on this test. As has been done in other ELSA studies (Gale et al., 2015; Kobayashi et al., 2014), scores on the ELSA health literacy test were categorised into adequate (scoring 4/4 correct) and limited (scoring less than 4 correct) health literacy. Although this test is brief and has limited variance, it has been found to be associated with various aspects of health including uptake of cancer screening, health behaviours, and mortality (Bostock & Steptoe, 2012; Kobayashi et al., 2014; Kobayashi et al., 2016b). In the current thesis, this heath literacy test was sensitive to associations with smoking status, diabetes status and polygenic profiles for cognitive ability and health-related traits. Therefore, despite its brief nature, this test appears to be measuring an important correlate of health. More detailed and continuous measures of health literacy might have been even more sensitive to associations with health, especially when using relatively healthy (and therefore relatively able) community-dwelling participants, as was done in ELSA.

Compared to the ELSA health literacy test, Chapter 6 used more detailed measures of health literacy to investigate the attenuating effect of cognitive ability in the association between health literacy and mortality using the LBC1936 sample. In this study, three of the most commonly used tests of health literacy were used: the S-TOFHLA, REALM, and Newest Vital Sign. In addition to examining the association between these health literacy tests and mortality separately, a general measure of health literacy was created by entering scores on the three tests into a principal component analysis and saving the scores from the first principal component. The aim here was to try create a more comprehensive measure of health literacy and to capture the shared variance between these tests (Mõttus et al., 2014). Compared to the brief health literacy test used in Chapters 4 and 5, this more detailed measure of health literacy is likely to be a more accurate representation of the construct of health literacy. Using the general health literacy measure used in Chapter 6, the green circle in Figure 8.2 would likely be much larger and closer in size to the yellow circle representing the health literacy construct.

If health literacy and cognitive ability are separate (though overlapping) constructs, and both health literacy and cognitive ability are assessed using comprehensive tests (e.g., the size of the green and blue circles in Figure 8.2 is close in size to the yellow and red circles representing the health literacy and cognitive ability constructs), one would expect to find that health literacy and cognitive ability both have independent associations with health. This is not what was found in Chapter 6. Instead, adjusting for a relatively detailed measure of cognitive ability attenuated and nullified the association between health literacy and health. These results could indicate that health literacy and cognitive ability form part of the same underlying mental ability (Gottfredson, 2004; Gottfredson & Deary, 2004; Reeve & Basalik, 2014). Alternatively, if health literacy and cognitive ability are independent constructs, it could indicate that the measure of health literacy used in Chapter 6 did not adequately assess all aspects of the health literacy construct.

As detailed in Section 1.3.4, the S-TOFHLA, REALM and Newest Vital Sign have been criticised because they only assess functional health literacy; that is, health-related reading comprehension and numeracy (Dumenci et al., 2013; Jordan et al., 2011). Health literacy is assumed to be a multidimensional construct and consist of range of skills and abilities needed to make appropriate decisions regarding one's health (Sørensen et al., 2012). Functional health literacy is thought to be only part of this larger construct (Dumenci et al., 2013; Jordan et al., 2011; Sørensen et al., 2012). In Chapter 6, the attenuation between health literacy and mortality seen when adjusting for fluid ability may be because the health literacy tests only assessed one part of health literacy—functional health literacy—and functional health literacy is the part of the health literacy construct which overlaps with cognitive ability.

More detailed measures of health literacy, such as the Health Literacy Questionnaire (HLQ; Osborne et al., 2013) and the European Health Literacy Survey Questionnaire (HLS-EU-Q; Sørensen et al., 2013), have been designed to assess health-related skills beyond functional health literacy. If health literacy is a separate construct from cognitive ability, these subjective health literacy assessments may be a more accurate measure of the health literacy construct. The relationship between these more detailed subjective tests of health literacy, cognitive ability and health has not been investigated.

Although the findings are not conclusive, the evidence reported in this thesis is most consistent with the conclusion that tests of health literacy and cognitive ability are entirely overlapping constructs. However, given the limitations of the health literacy and cognitive ability measures used in this thesis and in previous research, one cannot rule out the possibility that health literacy and cognitive ability may be partly overlapping, but partly separate constructs. Studies that examine the association between health literacy, cognitive ability and health, using measures of health literacy that assess all aspects of the multidimensional construct of health literacy—not just functional health literacy—are needed to be able to fully understand the relationship between health literacy and cognitive ability.

8.3.2.1. A comprehensive health literacy assessment

What would such a multidimensional assessment of health literacy look like? I propose that, to fully and comprehensively assess health literacy, health literacy assessments should mimic those often used to assess cognitive ability (Section 2.2). Cognitive ability is often assessed by getting participants to complete a large battery of validated cognitive tests that assess a range of different cognitive domains, such as processing speed, reasoning, executive function and declarative memory. Scores on a range of cognitive tests are then often combined into one composite score of general cognitive ability (*g*; Section 2.2). An ideal assessment of health literacy should likewise administer to participants a large battery of validated health literacy tests that assess a range of different components of health literacy. In addition to objective assessment of functional health literacy such as the TOFHLA, tests that assess health skills other than health-related reading and writing should be used. For example, another useful test to administer when trying to comprehensively assess health literacy would be the Comprehensive Health Activities Scale (Curtis et al., 2015), which measures the ability to understand verbal health information, as well as health-related reading and writing skills.

Health literacy is not simply being able to identify and understand health information. Another important component of health literacy is the ability to evaluate and apply health information (Sørensen et al., 2012). Self-reported assessments of health literacy, such as the HLS-EU-Q that is designed to assess the ability to access, understand, appraise and apply health information in many different areas of health (Sørensen et al., 2013), should also be included in a comprehensive assessment of health literacy.

Most measures of health literacy only consider the ability to understand and appraise traditional sources of health information, such as that provided by health professionals, or found on a health information leaflet. However, nowadays many people get their health information from other sources, including the on internet and via social media. Whereas the internet can be a useful source of finding reliable health information (e.g., NHS websites, and website for health charities such as Chest Heart & Stroke Scotland), there is also a wealth of misinformation and 'advice' by individuals and organisations that are not health professionals (Chou, Oh, & Klein, 2018). An important contemporary health skill involves being able to identify and evaluate sources of health information online and to determine whether the information is from a reliable source. Some of the items in the HLS-EU-Q assess the general ability to appraise sources of health information (e.g., are you able to “judge how reliable health warnings are”; Sørensen et al., 2013); however, no health literacy test explicitly assesses a participant’s ability to critique contemporary sources of health information including information available on the internet or on social media. To comprehensively measure all aspects of the multidimensional construct of health literacy, new health literacy tests may also be required that assess contemporary health-related skills.

The results of this thesis are most consistent with the conclusion that health literacy and cognitive ability are assessing the same underlying construct. However, the studies reported in this thesis and elsewhere are limited because health literacy may not have been comprehensively assessed in these studies. To confirm whether health literacy and cognitive ability are entirely overlapping constructs, future studies that examine the relationship between health literacy and cognitive ability using comprehensive assessments of both health literacy and cognitive ability are needed.

8.4. Limitations

The empirical work presented in this thesis has some limitations. Study specific limitations have already been discussed in each respective chapter. The limitations associated with the health literacy and cognitive ability measures used in this thesis have also been discussed in detail in Sections 8.2 and 8.3.2. One limitation is that the samples used in this thesis, like all cohort studies, are likely to suffer from sample bias and selective attrition (Salthouse, 2010b). Participants who agree to take part in research and return for repeat assessments tend to be the most able and healthiest members of society (Salthouse, 2010b). It is unlikely that the samples used in this thesis are assessing the full spectrum of health. By using relatively healthy community-dwelling samples, those with the poorest health may not have been represented. Those with the poorest health may also be those with the lowest health literacy and the lowest cognitive ability. Therefore, the results reported in this thesis may not generalise to those with the poorest health.

A related issue is that many of the health literacy tests used here were designed for use with clinical populations as a method of identifying patients who may have difficulties performing basic health tasks (Sørensen et al., 2012; Sørensen et al., 2013). With the exception of the Newest Vital Sign, which showed more variance, all of the health literacy tests used in this thesis had negatively-skewed distributions. That is, most participants scored at or close to full marks on these tests. The participants who agreed to take part in ELSA and LBC1936 are unlikely to be those members of society who have severe difficulties performing basic health tasks. More appropriate health literacy tests for the samples used in this thesis would be those which are designed to measure health literacy in general populations (Sørensen et al., 2013) and that are sensitive to more subtle differences in health literacy.

The studies reported in this thesis have missing data. Data could be missing for a number of reasons. Participants may not have been able to complete some of the tasks because of physical limitations. For example, individuals with poor eyesight may not have been to complete tasks that required reading printed text, and participants with arthritis or other conditions limiting mobility may not have been able to complete tasks involving writing. Participants also may have refused to complete any of the tasks. It is likely that only the most capable individuals answered all questions and completed all tests that were relevant for this thesis. The range of some of the key variables used in this thesis are likely to be restricted to the higher end of the distribution and therefore the results reported here may not generalise to individuals with the lowest health literacy or the lowest cognitive ability levels.

Another limitation of this thesis concerns the covariates used in the empirical chapters, and the order in which these covariates were entered into the models. The use of different covariates in each of the chapters is a limitation. Whereas Chapter 4 only adjusted for demographic and socioeconomic variables (age, sex, educational, and occupational social class) when examining the associations of health literacy and cognitive ability with smoking status, Chapter 5—which examined the relationship between health literacy, cognitive ability and risk of diabetes—additionally adjusted for health behaviours and cardiovascular comorbidities. On the other hand, Chapter 6, which investigated the role of cognitive ability in the association between health literacy and mortality, adjusted for self-reported measures of physical and mental health, but did not consider health behaviours, which may be an important mediator in the association between health literacy and mortality. Even when the same covariates were used, they were not always entered into the models in the same order. For example, education was introduced early in the model order (model 2) in Chapter 6, whereas it was not introduced until the final model (model 6) in Chapter 5. With regard to Chapter 6, during the peer review process, an expert reviewer suggested that education must be added to the models early because it has strong correlations with both health literacy and cognitive ability. Following these reviewer comments, the models in Chapter 6 were updated so that education was adjusted in model 2, whereas it had previously been added only after additionally adjusting for age, sex, age 11 IQ, and fluid ability in older age. As different covariates were entered in each analysis in different orders it makes it difficult to compare the results across each of the studies reported in this thesis.

A hierarchical approach to entering covariates was used in the models reported in Chapters 4, 5, and 6. The main reason for using this hierarchical approach was to try to determine which covariates may attenuate the association between health literacy and health, and cognitive ability and health. For example, in Chapter 5, health literacy and cognitive ability were first entered separately in models 1 and 2, adjusting only for age and sex. These minimally adjusted models were used to determine the size of the association of health literacy and cognitive ability with diabetes, before accounting for each other, and before adjusting for indicators of socioeconomic status and other aspects of health. Health literacy and cognitive ability were added together in model 3, along with age and sex. This was done to determine the change in the size of the association between health literacy and diabetes, and cognitive ability and diabetes, when also adjusting for the other variable.

Next, BMI and health behaviours were additionally added in model 4 with the aim of determining whether variables associated with a healthy lifestyle (e.g., maintaining a healthy weight, regular physical activity, not smoking, and moderate drinking) attenuated the association between health literacy and cognitive ability with diabetes. Model 5 additionally adjusted for cardiovascular comorbidities. Diabetes is itself a cardiovascular risk factor. Model 5 was used to examine whether the associations between health literacy and cognitive ability with diabetes were attenuated when additionally adjusting for other cardiovascular risk factors. It was assumed that if the associations between health literacy and cognitive ability with diabetes were attenuated when additionally adjusting for cardiovascular risk factors, then this would suggest that health literacy and cognitive ability were associated with cardiovascular risk and not specifically with diabetes. Health literacy, cognitive ability and diabetes are all related to socioeconomic status, therefore, the fully-adjusted model (model 6) also adjusted for education and occupational social class, to determine whether these indicators of socioeconomic status attenuated the associations between health literacy and cognitive ability with diabetes.

When BMI and health behaviours were added to model 4, the size of the association between health literacy and cognitive ability with diabetes status was reduced. In model 5, when cardiovascular comorbidities were additionally added to the model, the size of these associations remained very similar to that reported in model 4. When additionally adjusting for education and social class in model 6, the associations between health literacy and cognitive ability with diabetes were further reduced. I concluded in Chapter 5 (and Section 8.2.2) that this suggests that health behaviours and socioeconomic status, but not cardiovascular comorbidities, attenuate the association of health literacy and cognitive ability with diabetes. However, using hierarchical modelling, it is not possible to tell how much the addition of each group of covariates attenuates the association between health literacy and cognitive ability with diabetes. This is because some of the influence of each group of covariates (e.g., cardiovascular comorbidities) may be partly explained by other variables already entered in the model (e.g., BMI and health behaviours). This is a limitation of the studies reported in this thesis.

A more appropriate method to determine the size of the attenuation by each of the different groups of covariates would have been to adjust for each group of covariates individually, along with age and sex. Using this method, model 4 in Chapter 5 would have adjusted for age, sex, and health behaviours; model 5 would have adjusted for age, sex, and cardiovascular comorbidities; and model 6 would have adjusted for age, sex, and indicators of socioeconomic status. This type of modelling is required to be able to determine the size of the attenuation by each group of covariates in the association between health literacy and cognitive ability with diabetes. A final, fully-adjusted, model could then have been run adjusting for all covariates, to determine the size of the association between health literacy and cognitive ability with diabetes when accounting for all covariates simultaneously.

8.5. Implications

Regardless of whether tests of health literacy and cognitive ability are separate or overlapping constructs, this thesis adds to the growing literature that shows that individuals who have lower scores on tests of health literacy and tests of cognitive ability have poorer health. It is assumed that these tests of health literacy and cognitive ability are assessing important mental skills that are required to successfully self-manage health (Gottfredson, 2004; von Wagner et al., 2009). Managing health—both preventing and managing disease—is a cognitively complex task (Gottfredson, 2004). Rather than being unwilling to follow health advice and self-manage their health, participants with lower scores on tests of health literacy and cognitive ability might tend to be less capable of understanding and following health advice, because they tend to lack the mental capabilities required to optimally look after their health (Gottfredson & Deary, 2004).

Interventions have been designed to attempt to improve health literacy and cognitive ability (Blazer et al., 2015; Visscher et al., 2018). Cognitive ability is a relatively stable trait with respect to its individual differences from childhood to older age (Deary, 2014). Health literacy may also be relatively stable throughout life (Nutbeam, 2000). Instead of trying to identify methods to increase levels of cognitive ability and health literacy as a bid to improve health, interventions might more usefully focus on finding methods that increase understanding and make it easier for individuals with lower health literacy and/or cognitive ability to make appropriate health decisions (Gottfredson, 2004; Visscher et al., 2018; Wolf et al., 2009; World Health Organisation, 2013). That is, efforts might be more effectively aimed at making healthcare a less difficult set of cognitive tasks.

8.6. Future research

It is difficult to compare the results of the studies carried out in this thesis because some studies (Chapters 4, 5 and 7) have used relatively brief measures of health literacy and cognitive ability, whereas others (Chapter 6) have used more and/or more detailed tests. To more fully understand whether health literacy and cognitive ability have independent associations with health it is necessary for future studies to examine the relationship between health literacy, cognitive ability and health using comprehensive measures of both health literacy and cognitive ability. It is not clear whether the self-reported measures of health literacy, such as the HLQ (Osborne et al., 2013) and the HLS-EU-Q (Sørensen et al., 2013), that are designed to assess a much broader set of health literacy capabilities, have correlations with cognitive ability that are similar in strength to the correlations between cognitive ability and tests of functional health literacy. Future studies should examine the relationship between the HLQ and HLS-EU-Q with comprehensive measures of general cognitive ability and should assess whether health literacy, as measured by these more comprehensive tests, have associations with health independent of cognitive ability.

Although this thesis investigated whether health literacy and cognitive ability had associations with health that were independent of other health and socioeconomic variables, it did not formally test whether health- and socioeconomic-related variables mediated the associations of health literacy and cognitive ability with health. To better understand the possible pathways between health literacy, cognitive ability and health, future studies should investigate the mediating role of health behaviours and socioeconomic status in the relationship between health literacy and cognitive ability with health outcomes.

In this thesis, health literacy and cognitive ability were used as predictors of health. Health literacy and cognitive ability levels may also be outcomes of poor health. This was not considered in this thesis. For cognitive ability, there is evidence that lower cognitive ability is associated with increased risk of developing chronic diseases, such as diabetes or hypertension (Batty, Deary, et al., 2007a; Mõttus et al., 2013; Starr et al., 2004; Twig et al., 2014; Wraw et al., 2015). Diabetes and hypertension have, in turn, been associated with steeper cognitive decline (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006; Cukierman, Gerstein, & Williamson, 2005; Plassman, Williams, Burke, Holsinger, & Benjamin, 2010). It is possible that a similar association is seen for health literacy. That is, health literacy may both predict poor health, and may also decline as a result of poor health. However, there is evidence that those with more chronic disease experience (i.e., those that have had a chronic condition for longer) know more about their disease despite also having lower levels of cognitive ability (Chin et al., 2009). An alternative possibility is that health literacy and cognitive ability might have different longitudinal trajectories in people with a chronic disease. Chronic diseases such as diabetes might lead to a decline in cognitive ability but an increase in health literacy as those individuals who have had a chronic disease for many years might learn more about their disease and health in general, how to manage their chronic disease, and how to navigate the healthcare system (Chin et al., 2009). As another method to explore whether health literacy and cognitive ability are separate constructs, future studies should examine the longitudinal change in health literacy and cognitive ability in individuals with chronic disease.

The study reported in Chapter 7 was the first to investigate the molecular genetic contributions to health literacy. Whereas there was some evidence that health literacy shared genetic influences with cognitive ability and health, this study had a number of limitations (discussed in detail in Chapter 7) largely owing to the relatively small sample size. Future research should further explore the genetic influences of health literacy using much larger samples and using more detailed measures of health literacy. Future genetic studies should look to examine the genetic correlations between health literacy, cognitive ability and health to determine whether the genetic variants associated with health literacy overlap with the genetic variants associated with cognitive and health-related traits.

8.7. Final summary

This thesis sought to investigate whether health literacy and cognitive ability have independent associations with health. Three aspects of health were investigated; smoking status, diabetes status, and mortality. Better health literacy and higher cognitive ability were found to be independently associated with lower rates of smoking and a lower risk of diabetes; however, health literacy did not have associations with mortality that were independent of fluid ability. This thesis also investigated the genetic contributions to health literacy and found that genetic profiles for some cognitive and health-related traits were associated with performance on a health literacy test, providing additional support that cognitive ability, health literacy and health are intrinsically linked. It remains unclear whether health literacy and cognitive ability are assessing the same underlying construct;

however, the results of this thesis add to a growing body of evidence that those who perform poorly on tests of health literacy and tests of cognitive ability tend to have poorer health.

9. References

Ad Hoc Committee on Health Literacy for the Council on Scientific Affairs, & American Medical Association. (1999). Health literacy: report of the Council on Scientific Affairs. *JAMA, 281*(6), 552-557.

Adams, R. J., Appleton, S. L., Hill, C. L., Dodd, M., Findlay, C., & Wilson, D. H. (2009). Risks associated with low functional health literacy in an Australian population. *Medical Journal of Australia, 191*(10), 530-534.

Al Sayah, F., Majumdar, S. R., Williams, B., Robertson, S., & Johnson, J. A. (2013). Health literacy and health outcomes in diabetes: a systematic review. *Journal of General Internal Medicine, 28*(3), 444-452.

Allender, S., Balakrishnan, R., Scarborough, P., Webster, P., & Rayner, M. (2009). The burden of smoking-related ill health in the UK. *Tobacco Control, 18*(4), 262-267.

Alosco, M. L., Spitznagel, M. B., van Dulmen, M., Raz, N., Cohen, R., Sweet, L. H., . . . Gunstad, J. (2012). Cognitive function and treatment adherence in older adults with heart failure. *Psychosomatic Medicine, 74*(9), 965-973.

Arozullah, A. M., Yarnold, P. R., Bennett, C. L., Soltysik, R. C., Wolf, M. S., Ferreira, R. M., . . . Davis, T. C. (2007). Development and validation of a short-form, rapid estimate of adult literacy in medicine. *Medical Care, 45*(11), 1026-1033.

Bains, S. S., & Egede, L. E. (2011). Associations between health literacy, diabetes knowledge, self-care behaviors, and glycemic control in a low income population with type 2 diabetes. *Diabetes Technology & Therapeutics, 13*(3), 335-341.

Baker, D. W., Parker, R. M., Williams, M. V., & Clark, W. S. (1998). Health literacy and the risk of hospital admission. *Journal of General Internal Medicine, 13*(12), 791-798.

Baker, D. W., Williams, M. V., Parker, R. M., Gazmararian, J. A., & Nurss, J. (1999). Development of a brief test to measure functional health literacy. *Patient Education and Counseling, 38*(1), 33-42.

Baker, D. W., Gazmararian, J. A., Sudano, J., & Patterson, M. (2000). The association between age and health literacy among elderly persons. *The Journals of Gerontology Series B Psychological Sciences and Social Sciences, 55*(6), S368-374.

Baker, D. W., Gazmararian, J. A., Sudano, J., Patterson, M., Parker, R. M., & Williams, M. V. (2002). Health literacy and performance on the Mini-Mental State Examination. *Aging and Mental Health, 6*(1), 22-29.

Baker, D. W. (2006). The meaning and the measure of health literacy. *Journal of General Internal Medicine, 21*(8), 878-883.

Baker, D. W., Wolf, M. S., Feinglass, J., Thompson, J. A., Gazmararian, J. A., & Huang, J. (2007). Health literacy and mortality among elderly persons. *Archives of Internal Medicine, 167*(14), 1503-1509.

Baker, D. W., Wolf, M. S., Feinglass, J., & Thompson, J. A. (2008). Health literacy, cognitive abilities, and mortality among elderly persons. *Journal of General Internal Medicine, 23*(6), 723-726.

Bass, P. F., 3rd, Wilson, J. F., & Griffith, C. H. (2003). A shortened instrument for literacy screening. *Journal of General Internal Medicine, 18*(12), 1036-1038.

Batty, G. D., Mortensen, E. L., Nybo Andersen, A. M., & Osler, M. (2005). Childhood intelligence in relation to adult coronary heart disease and stroke risk:

evidence from a Danish birth cohort study. *Paediatric and Perinatal Epidemiology, 19*(6), 452-459.
Batty, G. D., Deary, I. J., & Macintyre, S. (2006). Childhood IQ and life course socioeconomic position in relation to alcohol induced hangovers in adulthood: the Aberdeen children of the 1950s study. *Journal of Epidemiology and Community Health, 60*(10), 872-874.
Batty, G. D., Deary, I. J., & Gottfredson, L. S. (2007). Premorbid (early life) IQ and later mortality risk: Systematic review. *Annals of Epidemiology, 17*(4), 278-288.
Batty, G. D., Deary, I. J., & Macintyre, S. (2007). Childhood IQ in relation to risk factors for premature mortality in middle-aged persons: the Aberdeen Children of the 1950s study. *Journal of Epidemiology and Community Health, 61*(3), 241-247.
Batty, G. D., Deary, I. J., Schoon, I., & Gale, C. R. (2007a). Mental ability across childhood in relation to risk factors for premature mortality in adult life: the 1970 British Cohort Study. *Journal of Epidemiology and Community Health, 61*(11), 997-1003.
Batty, G. D., Deary, I. J., Schoon, I., & Gale, C. R. (2007b). Childhood mental ability in relation to food intake and physical activity in adulthood: the 1970 British Cohort Study. *Pediatrics, 119*(1), e38-45.
Batty, G. D., Gale, C. R., Mortensen, L. H., Langenberg, C., Shipley, M. J., & Deary, I. J. (2008). Pre-morbid intelligence, the metabolic syndrome and mortality: the Vietnam Experience Study. *Diabetologia, 51*(3), 436-443.
Batty, G. D., Wennerstad, K. M., Smith, G. D., Gunnell, D., Deary, I. J., Tynelius, P., & Rasmussen, F. (2009). IQ in early adulthood and mortality by middle age: cohort study of 1 million Swedish men. *Epidemiology, 20*(1), 100-109.
Bennett, I. M., Chen, J., Soroui, J. S., & White, S. (2009). The contribution of health literacy to disparities in self-rated health status and preventive health behaviors in older adults. *Annals of Family Medicine, 7*(3), 204-211.
Bennett, J. S., Boyle, P. A., James, B. D., & Bennett, D. A. (2012). Correlates of health and financial literacy in older adults without dementia. *BMC Geriatrics, 12*, 30.
Berkman, N. D., Davis, T. C., & McCormack, L. (2010). Health literacy: what is it? *Journal of Health Communication, 15 Suppl 2*, 9-19.
Berkman, N. D., Sheridan, S. L., Donahue, K. E., Halpern, D. J., & Crotty, K. (2011). Low health literacy and health outcomes: an updated systematic review. *Annals of Internal Medicine, 155*(2), 97-107.
Biessels, G. J., Staekenborg, S., Brunner, E., Brayne, C., & Scheltens, P. (2006). Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurology, 5*(1), 64-74.
Blazer, D. G., Yaffe, K., & Liverman, C. T. (2015). *Cognitive aging: Progress in understanding and opportunities for action*. Washington, DC: National Academies Press.
Boomsma, D., Busjahn, A., & Peltonen, L. (2002). Classical twin studies and beyond. *Nature Reviews Genetics, 3*(11), 872-882.
Bostock, S., & Steptoe, A. (2012). Association between low functional health literacy and mortality in older adults: longitudinal cohort study. *BMJ, 344*, e1602.
Boyle, P. A., Yu, L., Wilson, R. S., Segawa, E., Buchman, A. S., & Bennett, D. A. (2013). Cognitive decline impairs financial and health literacy among community-based older persons without dementia. *Psychology Aging, 28*(3), 614-624.
Bulik-Sullivan, B. K., Loh, P. R., Finucane, H. K., Ripke, S., Yang, J., Patterson, N., . . . Schizophrenia Working Group. (2015). LD Score regression distinguishes

confounding from polygenicity in genome-wide association studies. *Nature Genetics, 47*(3), 291-295.
Calvin, C. M., Deary, I. J., Fenton, C., Roberts, B. A., Der, G., Leckenby, N., & Batty, G. D. (2011). Intelligence in youth and all-cause-mortality: systematic review with meta-analysis. *International Journal of Epidemiology, 40*(3), 626-644.
Calvin, C. M., Batty, G. D., Der, G., Brett, C. E., Taylor, A., Pattie, A., . . . Deary, I. J. (2017). Childhood intelligence in relation to major causes of death in 68 year follow-up: prospective population study. *BMJ, 357*.
Carroll, J. B. (1993). *Human cognitive abilities: a survey of factor-analytic studies*. Cambridge: Cambridge University Press.
Caruso, R., Magon, A., Baroni, I., Dellafiore, F., Arrigoni, C., Pittella, F., & Ausili, D. (2018). Health literacy in type 2 diabetes patients: a systematic review of systematic reviews. *Acta Diabetologica, 55*(1), 1-12.
Cattell, R. B. (1943). The measurement of adult intelligence. *Psychological Bulletin, 40*(3), 153.
Cavanaugh, K. L., Wingard, R. L., Hakim, R. M., Eden, S., Shintani, A., Wallston, K. A., . . . Ikizler, T. A. (2010). Low health literacy associates with increased mortality in ESRD. *Journal of the American Society of Nephrology, 21*(11), 1979-1985.
Chew, L. D., Griffin, J. M., Partin, M. R., Noorbaloochi, S., Grill, J. P., Snyder, A., . . . Vanryn, M. (2008). Validation of screening questions for limited health literacy in a large VA outpatient population. *Journal of General Internal Medicine, 23*(5), 561-566.
Chin, J., D'Andrea, L., Morrow, D., Stine-Morrow, E. A., Conner-Garcia, T., Graumlich, J., & Murray, M. (2009). *Cognition and illness experience are associated with illness knowledge among older adults with hypertension.* Paper presented at the Proceedings of the Human Factors and Ergonomics Society Annual Meeting.
Chin, J., Morrow, D. G., Stine-Morrow, E. A., Conner-Garcia, T., Graumlich, J. F., & Murray, M. D. (2011). The process-knowledge model of health literacy: evidence from a componential analysis of two commonly used measures. *Journal of Health Communication, 16 Suppl 3*, 222-241.
Chou, W.-Y. S., Oh, A., & Klein, W. M. (2018). Addressing health-related misinformation on social media. *JAMA, 320*(23), 2417-2418.
Christensen, G. T., Mortensen, E. L., Christensen, K., & Osier, M. (2016). Intelligence in young adulthood and cause-specific mortality in the Danish Conscription Database - A Cohort study of 728,160 men. *Intelligence, 59*, 64-71.
Clouston, S. A. P., Manganello, J. A., & Richards, M. (2017). A life course approach to health literacy: the role of gender, educational attainment and lifetime cognitive capability. *Age and Ageing, 46*(3), 493-499.
Corley, J., Cox, S. R., & Deary, I. J. (2018). Healthy cognitive ageing in the Lothian Birth Cohort studies: marginal gains not magic bullet. *Psychological Medicine, 48*(2), 187-207.
Čukić, I., Brett, C. E., Calvin, C. M., Batty, G. D., & Deary, I. J. (2017). Childhood IQ and survival to 79: Follow-up of 94% of the Scottish Mental Survey 1947. *Intelligence, 63*, 45-50.
Cukierman, T., Gerstein, H. C., & Williamson, J. D. (2005). Cognitive decline and dementia in diabetes: systematic overview of prospective observational studies. *Diabetologia, 48*(12), 2460-2469.
Curtis, L. M., Revelle, W., Waite, K., Wilson, E. A., Condon, D. M., Bojarski, E., . . . Wolf, M. S. (2015). Development and validation of the comprehensive health

activities scale: a new approach to health literacy measurement. *Journal of Health Communication, 20*(2), 157-164.
Dahlke, A. R., Curtis, L. M., Federman, A. D., & Wolf, M. S. (2014). The mini mental status exam as a surrogate measure of health literacy. *Journal of General Internal Medicine, 29*(4), 615-620.
Davies, G., Tenesa, A., Payton, A., Yang, J., Harris, S. E., Liewald, D., . . . Deary, I. J. (2011). Genome-wide association studies establish that human intelligence is highly heritable and polygenic. *Molecular Psychiatry, 16*(10), 996-1005.
Davies, G., Lam, M., Harris, S. E., Trampush, J. W., Luciano, M., Hill, W. D., . . . Deary, I. J. (2018). Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. *Nature Communications, 9*, 2098.
Davis, T. C., Crouch, M. A., Long, S. W., Jackson, R. H., Bates, P., George, R. B., & Bairnsfather, L. E. (1991). Rapid assessment of literacy levels of adult primary care patients. *Family Medicine, 23*(6), 433-435.
Davis, T. C., Long, S. W., Jackson, R. H., Mayeaux, E., George, R. B., Murphy, P. W., & Crouch, M. A. (1993). Rapid estimate of adult literacy in medicine: a shortened screening instrument. *Family Medicine, 25*(6), 391-395.
Deary, I. J., Whalley, L. J., Lemmon, H., Crawford, J., & Starr, J. M. (2000). The stability of individual differences in mental ability from childhood to old age: follow-up of the 1932 Scottish Mental Survey. *Intelligence, 28*(1), 49-55.
Deary, I. J., & Batty, G. D. (2007). Cognitive epidemiology. *Journal of Epidemiology and Community Health, 61*(5), 378-384.
Deary, I. J., Gow, A. J., Taylor, M. D., Corley, J., Brett, C., Wilson, V., . . . Starr, J. M. (2007). The Lothian Birth Cohort 1936: a study to examine influences on cognitive ageing from age 11 to age 70 and beyond. *BMC Geriatrics, 7*, 28.
Deary, I. J., Strand, S., Smith, P., & Fernandes, C. (2007). Intelligence and educational achievement. *Intelligence, 35*(1), 13-21.
Deary, I. J., Penke, L., & Johnson, W. (2010). The neuroscience of human intelligence differences. *Nature Reviews Neuroscience, 11*(3), 201-211.
Deary, I. J., Weiss, A., & Batty, G. D. (2010). Intelligence and Personality as Predictors of Illness and Death: How Researchers in Differential Psychology and Chronic Disease Epidemiology Are Collaborating to Understand and Address Health Inequalities. *Psychological Science in the Public Interest, 11*(2), 53-79.
Deary, I. J. (2012). Looking for 'system integrity' in cognitive epidemiology. *Gerontology, 58*(6), 545-553.
Deary, I. J., Gow, A. J., Pattie, A., & Starr, J. M. (2012). Cohort profile: the Lothian Birth Cohorts of 1921 and 1936. *International Journal of Epidemiology, 41*(6), 1576-1584.
Deary, I. J., Pattie, A., & Starr, J. M. (2013). The stability of intelligence from age 11 to age 90 years: the Lothian birth cohort of 1921. *Psychological Science, 24*(12), 2361-2368.
Deary, I. J. (2014). The stability of intelligence from childhood to old age. *Current Directions in Psychological Science, 23*(4), 239-245.
Deary, I. J., Harris, S. E., & Hill, W. D. (2019). What genome-wide association studies reveal about the association between intelligence and physical health, illness, and mortality. *Current Opinion in Psychology, 27*, 6-12.
Delis, D. C., Kramer, J. H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the Delis-Kaplan Executive Function System: an update. *Journal of the International Neuropsychological Society, 10*(2), 301-303.

Der, G., Batty, G. D., & Deary, I. J. (2009). The association between IQ in adolescence and a range of health outcomes at 40 in the 1979 US National Longitudinal Study of Youth. *Intelligence, 37*(6), 573-580.

Dewalt, D. A., Berkman, N. D., Sheridan, S., Lohr, K. N., & Pignone, M. P. (2004). Literacy and health outcomes: a systematic review of the literature. *Journal of General Internal Medicine, 19*(12), 1228-1239.

Diabetes UK. (2014). *Diabetes: Facts and stats* (Diabetes UK Ed.).

Dumenci, L., Matsuyama, R. K., Kuhn, L., Perera, R. A., & Siminoff, L. A. (2013). On the Validity of the Rapid Estimate of Adult Literacy in Medicine (REALM) Scale as a Measure of Health Literacy. *Communication Methods and Measures, 7*(2), 134-143.

Ekstrom, R. B., French, J. W., Harman, H. H., & Derman, D. (1976). *Manual for kit of factor-referenced cognitive tests*. Princeton, NJ: Educational Testing Service.

Fawns-Ritchie, C., Starr, J. M., & Deary, I. J. (2018a). Role of cognitive ability in the association between functional health literacy and mortality in the Lothian Birth Cohort 1936: a prospective cohort study. *BMJ Open, 8*(9), e022502.

Fawns-Ritchie, C., Starr, J. M., & Deary, I. J. (2018b). Health literacy, cognitive ability and smoking: a cross-sectional analysis of the English Longitudinal Study of Ageing. *BMJ Open, 8*(10), e023929.

Federman, A. D., Sano, M., Wolf, M. S., Siu, A. L., & Halm, E. A. (2009). Health literacy and cognitive performance in older adults. *Journal of the American Geriatrics Society, 57*(8), 1475-1480.

Fernandez, D. M., Larson, J. L., & Zikmund-Fisher, B. J. (2016). Associations between health literacy and preventive health behaviors among older adults: findings from the health and retirement study. *BMC Public Health, 16*, 596.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198.

Forman, J. P., Stampfer, M. J., & Curhan, G. C. (2009). Diet and lifestyle risk factors associated with incident hypertension in women. *JAMA, 302*(4), 401-411.

Gale, C. R., Hatch, S. L., Batty, G. D., & Deary, I. J. (2009). Intelligence in childhood and risk of psychological distress in adulthood: The 1958 National Child Development Survey and the 1970 British Cohort Study. *Intelligence, 37*(6), 592-599.

Gale, C. R., Batty, G. D., Tynelius, P., Deary, I. J., & Rasmussen, F. (2010). Intelligence in early adulthood and subsequent hospitalisation and admission rates for the whole range of mental disorders: longitudinal study of 1,049,663 men. *Epidemiology, 21*(1), 70-77.

Gale, C. R., Deary, I. J., Wardle, J., Zaninotto, P., & Batty, G. D. (2015). Cognitive ability and personality as predictors of participation in a national colorectal cancer screening programme: the English Longitudinal Study of Ageing. *Journal of Epidemiology and Community Health, 69*(6), 530-535.

Gardner, H. (1983). *Frames of mind: The theory of multiple intelligences*. New York, NY: Basic Books.

Gazmararian, J. A., Baker, D., Parker, R., & Blazer, D. G. (2000). A multivariate analysis of factors associated with depression: evaluating the role of health literacy as a potential contributor. *Archives of Internal Medicine, 160*(21), 3307-3314.

Gazmararian, J. A., Williams, M. V., Peel, J., & Baker, D. W. (2003). Health literacy and knowledge of chronic disease. *Patient Education and Counseling, 51*(3), 267-275.

Gottfredson, L. S. (1997). Mainstream science on intelligence: An editorial with 52 signatories, history, and bibliography. *Intelligence, 24*(1), 13-23.

Gottfredson, L. S. (2004). Intelligence: is it the epidemiologists' elusive "fundamental cause" of social class inequalities in health? *Journal of Personality and Social Psychology, 86*(1), 174-199.
Gottfredson, L. S., & Deary, I. J. (2004). Intelligence predicts health and longevity, but why? *Current Directions in Psychological Science, 13*(1), 1-4.
Guzys, D., Kenny, A., Dickson-Swift, V., & Threlkeld, G. (2015). A critical review of population health literacy assessment. *BMC Public Health, 15*, 215.
Hagenaars, S. P., Harris, S. E., Davies, G., Hill, W. D., Liewald, D. C. M., Ritchie, S. J., . . . Deary, I. J. (2016). Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N=112151) and 24 GWAS consortia. *Molecular Psychiatry, 21*(11), 1624-1632.
Hajduk, A. M., Lemon, S. C., McManus, D. D., Lessard, D. M., Gurwitz, J. H., Spencer, F. A., . . . Saczynski, J. S. (2013). Cognitive impairment and self-care in heart failure. *Clinical Epidemiology, 5*, 407-416.
Han, S. D., Boyle, P. A., James, B. D., Yu, L., & Bennett, D. A. (2015). Poorer Financial and Health Literacy Among Community-Dwelling Older Adults With Mild Cognitive Impairment. *Journal of Aging and Health, 27*(6), 1105-1117.
Hart, C. L., Taylor, M. D., Smith, G. D., Whalley, L. J., Starr, J. M., Hole, D. J., . . . Deary, I. J. (2004). Childhood IQ and cardiovascular disease in adulthood: prospective observational study linking the Scottish Mental Survey 1932 and the Midspan studies. *Social Science & Medicine, 59*(10), 2131-2138.
Haworth, C. M. A., Wright, M. J., Luciano, M., Martin, N. G., de Geus, E. J. C., van Beijsterveldt, C. E. M., . . . Plomin, R. (2010). The heritability of general cognitive ability increases linearly from childhood to young adulthood. *Molecular Psychiatry, 15*(11), 1112-1120.
Heinrichs, R. W., Goldberg, J. O., Miles, A. A., & McDermid Vaz, S. (2008). Predictors of medication competence in schizophrenia patients. *Psychiatry Research, 157*(1-3), 47-52.
Hemmingsson, T., Kriebel, D., Melin, B., Allebeck, P., & Lundberg, I. (2008). How does IQ affect onset of smoking and cessation of smoking--linking the Swedish 1969 conscription cohort to the Swedish survey of living conditions. *Psychosomatic Medicine, 70*(7), 805-810.
Hill, W. D., Harris, S. E., & Deary, I. J. (2019). What genome-wide association studies reveal about the association between intelligence and mental health. *Current Opinion in Psychology, 27*, 25-30.
Hinkin, C. H., Castellon, S. A., Durvasula, R. S., Hardy, D. J., Lam, M. N., Mason, K. I., . . . Stefaniak, M. (2002). Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity. *Neurology, 59*(12), 1944-1950.
Hinkin, C. H., Hardy, D. J., Mason, K. I., Castellon, S. A., Durvasula, R. S., Lam, M. N., & Stefaniak, M. (2004). Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS, 18 Suppl 1*(Suppl 1), S19-S25.
Horn, J. L. (1989). Models of intelligence. In R. L. Linn (Ed.), *Intelligence: Measurement, Theory, and Public Policy* (pp. 29-73). Urbana, IL: University of Illinois Press.
Horn, J. L. (1994). Theory of fluid and crystallized intelligence. In R. J. Sternberg (Ed.), *Encyclopedia of Human Intelligence* (pp. 443-451). New York: Macmillan.
Hsieh, S., Schubert, S., Hoon, C., Mioshi, E., & Hodges, J. R. (2013). Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders, 36*(3-4), 242-250.

Huai, P., Xun, H., Reilly, K. H., Wang, Y., Ma, W., & Xi, B. (2013). Physical activity and risk of hypertension: a meta-analysis of prospective cohort studies. *Hypertension, 62*(6), 1021-1026.
Hung, G. C.-L., Pietras, S. A., Carliner, H., Martin, L., Seidman, L. J., Buka, S. L., & Gilman, S. E. (2016). Cognitive ability in childhood and the chronicity and suicidality of depression. *The British Journal of Psychiatry, 208*(2), 120-127.
Hussain, A., Claussen, B., Ramachandran, A., & Williams, R. (2007). Prevention of type 2 diabetes: a review. *Diabetes Research and Clinical Practice, 76*(3), 317-326.
Insel, K., Morrow, D., Brewer, B., & Figueredo, A. (2006). Executive function, working memory, and medication adherence among older adults. *The Journals of Gerontology Series B Psychological Sciences and Social Sciences, 61*(2), P102-P107.
Ismail, Z., Rajji, T. K., & Shulman, K. I. (2010). Brief cognitive screening instruments: an update. *International Journal of Geriatric Psychiatry, 25*(2), 111-120.
Johnson, W., Bouchard Jr, T. J., Krueger, R. F., McGue, M., & Gottesman, I. I. (2004). Just one g: Consistent results from three test batteries. *Intelligence, 32*(1), 95-107.
Johnson, W., te Nijenhuis, J., & Bouchard, T. J. (2008). Still just 1 g: Consistent results from five test batteries. *Intelligence, 36*(1), 81-95.
Johnson, W., Corley, J., Starr, J. M., & Deary, I. J. (2011). Psychological and physical health at age 70 in the Lothian Birth Cohort 1936: links with early life IQ, SES, and current cognitive function and neighborhood environment. *Health Psychology, 30*(1), 1-11.
Jordan, J. E., Osborne, R. H., & Buchbinder, R. (2011). Critical appraisal of health literacy indices revealed variable underlying constructs, narrow content and psychometric weaknesses. *Journal of Clinical Epidemiology, 64*(4), 366-379.
Kaphingst, K. A., Goodman, M. S., MacMillan, W. D., Carpenter, C. R., & Griffey, R. T. (2014). Effect of cognitive dysfunction on the relationship between age and health literacy. *Patient Education and Counseling, 95*(2), 218-225.
Kaup, A. R., Simonsick, E. M., Harris, T. B., Satterfield, S., Metti, A. L., Ayonayon, H. N., . . . Yaffe, K. (2014). Older adults with limited literacy are at increased risk for likely dementia. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 69*(7), 900-906.
Kobayashi, L. C., Wardle, J., & von Wagner, C. (2014). Limited health literacy is a barrier to colorectal cancer screening in England: evidence from the English Longitudinal Study of Ageing. *Preventive Medicine, 61*, 100-105.
Kobayashi, L. C., Smith, S. G., O'Conor, R., Curtis, L. M., Park, D., von Wagner, C., . . . Wolf, M. S. (2015). The role of cognitive function in the relationship between age and health literacy: a cross-sectional analysis of older adults in Chicago, USA. *BMJ Open, 5*(4), e007222.
Kobayashi, L. C., Wardle, J., Wolf, M. S., & von Wagner, C. (2016a). Aging and Functional Health Literacy: A Systematic Review and Meta-Analysis. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 71*(3), 445-457.
Kobayashi, L. C., Wardle, J., Wolf, M. S., & von Wagner, C. (2016b). Health Literacy and Moderate to Vigorous Physical Activity During Aging, 2004-2013. *American Journal of Preventive Medicine, 51*(4), 463-472.
Koenen, K. C., Moffitt, T. E., Roberts, A. L., Martin, L. T., Kubzansky, L., Harrington, H., . . . Caspi, A. (2009). Childhood IQ and adult mental disorders: a test of the cognitive reserve hypothesis. *American Journal of Psychiatry, 166*(1), 50-57.

Lamar, M., Wilson, R. S., Yu, L., James, B. D., Stewart, C. C., Bennett, D. A., & Boyle, P. A. (2019). Associations of literacy with diabetes indicators in older adults. *Journal of Epidemiology and Community Health, 73*(3), 250-255.
Lara, J., Cooper, R., Nissan, J., Ginty, A. T., Khaw, K. T., Deary, I. J., . . . Mathers, J. C. (2015). A proposed panel of biomarkers of healthy ageing. *BMC Medicine, 13*, 222.
Luciano, M., Weiss, A., Gale, C. R., & Deary, I. D. (2018). Personality, intelligence and genes. In M. Kivimäki, D. Batty, I. Kawachi, & A. Steptoe (Eds.), *The Routledge International Handbook of Psychosocial Epidemiology* Oxon, UK: Routledge.
Macabasco-O'Connell, A., DeWalt, D. A., Broucksou, K. A., Hawk, V., Baker, D. W., Schillinger, D., . . . Pignone, M. (2011). Relationship between literacy, knowledge, self-care behaviors, and heart failure-related quality of life among patients with heart failure. *Journal of General Internal Medicine, 26*(9), 979-986.
Mancuso, J. M. (2009). Assessment and measurement of health literacy: an integrative review of the literature. *Nursing & Health Sciences, 11*(1), 77-89.
Marciano, L., Camerini, A. L., & Schulz, P. J. (2019). The Role of Health Literacy in Diabetes Knowledge, Self-Care, and Glycemic Control: a Meta-analysis. *Journal of General Internal Medicine, 34*(6), 1007-1017.
Martin, L. T., Fitzmaurice, G. M., Kindlon, D. J., & Buka, S. L. (2004). Cognitive performance in childhood and early adult illness: a prospective cohort study. *Journal of Epidemiology and Community Health, 58*(8), 674-679.
Mathers, J. C., Deary, I. J., Kuh, D., Lord, J. M., Khaw, K. T., Lara, J., . . . Ginty, A. (2015). *Guidelines for biomarkers of healthy ageing*. Medical Research Council

Retrieved from https://mrc.ukri.org/documents/pdf/biomarkers-of-healthy-ageing/.
Mõttus, R., Luciano, M., Starr, J. M., & Deary, I. J. (2013). Diabetes and life-long cognitive ability. *Journal of Psychosomatic Research, 75*(3), 275-278.
Mõttus, R., Johnson, W., Murray, C., Wolf, M. S., Starr, J. M., & Deary, I. J. (2014). Towards understanding the links between health literacy and physical health. *Health Psychology, 33*(2), 164-173.
Murray, C., Johnson, W., Wolf, M. S., & Deary, I. J. (2011). The Association between Cognitive Ability across the Lifespan and Health Literacy in Old Age: The Lothian Birth Cohort 1936. *Intelligence, 39*(4), 178-187.
Nguyen, H. T., Kirk, J. K., Arcury, T. A., Ip, E. H., Grzywacz, J. G., Saldana, S. J., . . . Quandt, S. A. (2013). Cognitive function is a risk for health literacy in older adults with diabetes. *Diabetes Research and Clinical Practice, 101*(2), 141-147.
Nielsen-Bohlman, L., Panzer, A. M., & Kindig, D. A. (2004). *Health Literacy: A Prescription to End Confusion*. Washinton, DC: The National Academies Press.
Nutbeam, D. (2000). Health literacy as a public health goal: a challenge for contemporary health education and communication strategies into the 21st century. *Health Promotion International, 15*(3), 259-267.
Nutbeam, D. (2008). The evolving concept of health literacy. *Social Science & Medicine, 67*(12), 2072-2078.
O'Conor, R., Wolf, M. S., Smith, S. G., Martynenko, M., Vicencio, D. P., Sano, M., . . . Federman, A. D. (2015). Health literacy, cognitive function, proper use, and adherence to inhaled asthma controller medications among older adults with asthma. *Chest, 147*(5), 1307-1315.

O'Conor, R., Muellers, K., Arvanitis, M., Vicencio, D. P., Wolf, M. S., Wisnivesky, J. P., & Federman, A. D. (2019). Effects of health literacy and cognitive abilities on COPD self-management behaviors: A prospective cohort study. *Respiratory Medicine*.

Office for National Statistics. (2017). *Adult smoking habits in the UK: 2016*. Retrieved from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2016: Public Health England

Oldach, B. R., & Katz, M. L. (2014). Health literacy and cancer screening: a systematic review. *Patient Education and Counseling, 94*(2), 149-157.

Oliveira, D., Bosco, A., & di Lorito, C. (2019). Is poor health literacy a risk factor for dementia in older adults? Systematic literature review of prospective cohort studies. *Maturitas, 124*, 8-14.

Osborn, C. Y., Paasche-Orlow, M. K., Bailey, S. C., & Wolf, M. S. (2011). The mechanisms linking health literacy to behavior and health status. *American Journal of Health Behavior, 35*(1), 118-128.

Osborne, R. H., Batterham, R. W., Elsworth, G. R., Hawkins, M., & Buchbinder, R. (2013). The grounded psychometric development and initial validation of the Health Literacy Questionnaire (HLQ). *BMC Public Health, 13*, 658.

Ownby, R. L., Acevedo, A., Waldrop-Valverde, D., Jacobs, R. J., & Caballero, J. (2014). Abilities, skills and knowledge in measures of health literacy. *Patient Education and Counseling, 95*(2), 211-217.

Paasche-Orlow, M. K., & Wolf, M. S. (2007). The causal pathways linking health literacy to health outcomes. *American Journal of Health Behavior, 31 Suppl 1*, S19-26.

Paasche-Orlow, M. K., Parker, R. M., Gazmararian, J. A., Nielsen-Bohlman, L. T., & Rudd, R. R. (2005). The prevalence of limited health literacy. *Journal of General Internal Medicine, 20*(2), 175-184.

Parker, R. M., Baker, D. W., Williams, M. V., & Nurss, J. R. (1995). The test of functional health literacy in adults: A new instrument for measuring patients' literacy skills. *Journal of General Internal Medicine, 10*(10), 537-541.

Parker, R. M., Wolf, M. S., & Kirsch, I. (2008). Preparing for an epidemic of limited health literacy: weathering the perfect storm. *Journal of General Internal Medicine, 23*(8), 1273-1276.

Parker, R. M., & Ratzan, S. C. (2010). Health literacy: a second decade of distinction for Americans. *Journal of Health Communication, 15 Suppl 2*, 20-33.

Peterson, N. B., Dwyer, K. A., Mulvaney, S. A., Dietrich, M. S., & Rothman, R. L. (2007). The influence of health literacy on colorectal cancer screening knowledge, beliefs and behavior. *Journal of the National Medical Association, 99*(10), 1105-1112.

Pierce, M. B., Zaninotto, P., Steel, N., & Mindell, J. (2009). Undiagnosed diabetes-data from the English longitudinal study of ageing. *Diabetic Medicine, 26*(7), 679-685.

Plassman, B. L., Williams, J. W., Jr., Burke, J. R., Holsinger, T., & Benjamin, S. (2010). Systematic review: factors associated with risk for and possible prevention of cognitive decline in later life. *Annals of Internal Medicine, 153*(3), 182-193.

Plomin, R., & Deary, I. J. (2015). Genetics and intelligence differences: five special findings. *Molecular Psychiatry, 20*(1), 98-108.

Polderman, T. J. C., Benyamin, B., de Leeuw, C. A., Sullivan, P. F., van Bochoven, A., Visscher, P. M., & Posthuma, D. (2015). Meta-analysis of the heritability

of human traits based on fifty years of twin studies. *Nature Genetics, 47*(7), 702-709.
Powell, C. K., Hill, E. G., & Clancy, D. E. (2007). The relationship between health literacy and diabetes knowledge and readiness to take health actions. *Diabetes Educator, 33*(1), 144-151.
Protheroe, J., Nutbeam, D., & Rowlands, G. (2009). Health literacy: a necessity for increasing participation in health care. *British Journal of General Practice, 59*(567), 721-723.
Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., & Sklar, P. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature, 460*(7256), 748-752.
Ratzan, S. C., & Parker, R. M. (2000). Introduction. In C. R. Selden, M. Zorn, S. C. Ratzan, & R. M. Parker (Eds.), *National Library of Medicine Current Bibliographies in Medicine: Health Literacy*. Bethesda, MD.: National Insttitues of Health, U.S Department of Health and Human Services.
Reeve, C. L., & Basalik, D. (2014). Is health literacy an example of construct proliferation? A conceptual and empirical evaluation of its redundancy with general cognitive ability. *Intelligence, 44*, 93-102.
Rose, D., Pevalin, D. J., & O'Reilly, K. (2005). *The National Statistics Socio-economic Classification: origins, development and use*: Palgrave Macmillan Basingstoke.
Rosen, M. I., Beauvais, J. E., Rigsby, M. O., Salahi, J. T., Ryan, C. E., & Cramer, J. A. (2003). Neuropsychological correlates of suboptimal adherence to metformin. *Journal of Behavioral Medicine, 26*(4), 349-360.
Rostamian, S., Mahinrad, S., Stijnen, T., Sabayan, B., & de Craen, A. J. (2014). Cognitive impairment and risk of stroke: a systematic review and meta-analysis of prospective cohort studies. *Stroke, 45*(5), 1342-1348.
Ruch, W. W., Stang, S. W., McKillip, R. H., & Dye, M. (2001). *Employee Aptitude Survey Technical Manual (2nd ed.)* Glendale, CA.: Psychological Services, Inc.
Rudd, R., Moeykens, B., & Colton, T. (2000). Health and literacy. A review of medical and public health literature. In J. Comings, B. Garners, & C. Smith (Eds.), *Annual Review of Adult Learning and Literacy*. New York: Jossy-Bass.
Salas, M., In't Veld, B. A., van der Linden, P. D., Hofman, A., Breteler, M., & Stricker, B. H. (2001). Impaired cognitive function and compliance with antihypertensive drugs in elderly: the Rotterdam Study. *Clinical Pharmacology and Therapeutics, 70*(6), 561-566.
Salthouse, T. A. (2004). Localizing age-related individual differences in a hierarchical structure. *Intelligence, 32*(6), 541-561.
Salthouse, T. A. (2010a). Selective review of cognitive aging. *Journal of the International Neuropsychological Society, 16*(5), 754-760.
Salthouse, T. A. (2010b). *Major issues in cognitive ageing*. Oxford: Oxford University Press.
Salthouse, T. A. (2012). Consequences of age-related cognitive declines. *Annual Review of Psychology, 63*, 201-226.
Sarwar, N., Gao, P., Seshasai, S. R., Gobin, R., Kaptoge, S., Di Angelantonio, E., . . . Danesh, J. (2010). Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet, 375*(9733), 2215-2222.
Savage, J. E., Jansen, P. R., Stringer, S., Watanabe, K., Bryois, J., de Leeuw, C. A., . . . Posthuma, D. (2018). Genome-wide association meta-analysis in

269,867 individuals identifies new genetic and functional links to intelligence. *Nature Genetics, 50*(7), 912-919.
Schaie, K. W. (1996). *Intellectual development in adulthood: The Seattle longitudinal study*. Cambridge: Cambridge University Press.
Schillinger, D., Grumbach, K., Piette, J., Wang, F., Osmond, D., Daher, C., . . . Bindman, A. B. (2002). Association of health literacy with diabetes outcomes. *JAMA, 288*(4), 475-482.
Serper, M., Patzer, R. E., Curtis, L. M., Smith, S. G., Conor, R., Baker, D. W., & Wolf, M. S. (2014). Health Literacy, Cognitive Ability, and Functional Health Status among Older Adults. *Health Services Research, 49*(4), 1249-1267.
Shaw, A., Ibrahim, S., Reid, F., Ussher, M., & Rowlands, G. (2009). Patients' perspectives of the doctor-patient relationship and information giving across a range of literacy levels. *Patient Education and Counseling, 75*(1), 114-120.
Simonds, S. (1974). Health education as social policy. *Health Education Monograph, 2*, 1-25.
Sørensen, K., Van den Broucke, S., Fullam, J., Doyle, G., Pelikan, J., Slonska, Z., . . . European, H.-E. C. H. L. P. (2012). Health literacy and public health: a systematic review and integration of definitions and models. *BMC Public Health, 12*, 80.
Sørensen, K., Van den Broucke, S., Pelikan, J. M., Fullam, J., Doyle, G., Slonska, Z., . . . Brand, H. (2013). Measuring health literacy in populations: illuminating the design and development process of the European Health Literacy Survey Questionnaire (HLS-EU-Q). *BMC Public Health, 13*(1), 948.
Sørensen, K., Pelikan, J. M., Rothlin, F., Ganahl, K., Slonska, Z., Doyle, G., . . . Brand, H. (2015). Health literacy in Europe: comparative results of the European health literacy survey (HLS-EU). *European Journal of Public Health, 25*(6), 1053-1058.
Spearman, C. (1904). "General Intelligence", objectively determined and measured. *The American Journal of Psychology, 15*(2), 201-292.
Starr, J. M., Taylor, M. D., Hart, C. L., Davey Smith, G., Whalley, L. J., Hole, D. J., . . . Deary, I. J. (2004). Childhood mental ability and blood pressure at midlife: linking the Scottish Mental Survey 1932 and the Midspan studies. *Journal of Hypertension, 22*(5), 893-897.
Steptoe, A., Breeze, E., Banks, J., & Nazroo, J. (2013). Cohort profile: the English longitudinal study of ageing. *International Journal of Epidemiology, 42*(6), 1640-1648.
Stilley, C. S., Sereika, S., Muldoon, M. F., Ryan, C. M., & Dunbar-Jacob, J. (2004). Psychological and cognitive function: predictors of adherence with cholesterol lowering treatment. *Annals of Behavioral Medicine, 27*(2), 117-124.
Stilley, C. S., Bender, C. M., Dunbar-Jacob, J., Sereika, S., & Ryan, C. M. (2010). The impact of cognitive function on medication management: three studies. *Health Psychology, 29*(1), 50-55.
Strenze, T. (2007). Intelligence and socioeconomic success: A meta-analytic review of longitudinal research. *Intelligence, 35*, 401-426.
Sudore, R. L., Yaffe, K., Satterfield, S., Harris, T. B., Mehta, K. M., Simonsick, E. M., . . . Schillinger, D. (2006). Limited literacy and mortality in the elderly: the health, aging, and body composition study. *Journal of General Internal Medicine, 21*(8), 806-812.
Tang, Y. H., Pang, S. M., Chan, M. F., Yeung, G. S., & Yeung, V. T. (2008). Health literacy, complication awareness, and diabetic control in patients with type 2 diabetes mellitus. *Journal of Advanced Nursing, 62*(1), 74-83.

Taylor, A. M., Pattie, A., & Deary, I. J. (2018). Cohort Profile Update: The Lothian Birth Cohorts of 1921 and 1936. *International Journal of Epidemiology, 47*(4), 1042-1042r.
Taylor, M. D., Hart, C. L., Davey Smith, G., Starr, J. M., Hole, D. J., Whalley, L. J., . . . Deary, I. J. (2003). Childhood mental ability and smoking cessation in adulthood: prospective observational study linking the Scottish Mental Survey 1932 and the Midspan studies. *Journal of Epidemiology and Community Health, 57*(6), 464-465.
Thorn, W. (2009). *International adult literacy and basic skills surveys in the OECD region*. Paris: OECD Publishing.
Thurstone, L. L. (1938). Primary mental abilities. *Psychometric Monographs, No. 1*.
Twig, G., Gluzman, I., Tirosh, A., Gerstein, H. C., Yaniv, G., Afek, A., . . . Cukierman-Yaffe, T. (2014). Cognitive function and the risk for diabetes among young men. *Diabetes Care, 37*(11), 2982-2988.
Twig, G., Tirosh, A., Derazne, E., Haklai, Z., Goldberger, N., Afek, A., . . . Cukierman-Yaffe, T. (2018). Cognitive function in adolescence and the risk for premature diabetes and cardiovascular mortality in adulthood. *Cardiovascular Diabetology, 17*(1), 154.
Visscher, B. B., Steunenberg, B., Heijmans, M., Hofstede, J. M., Deville, W., van der Heide, I., & Rademakers, J. (2018). Evidence on the effectiveness of health literacy interventions in the EU: a systematic review. *BMC Public Health, 18*(1), 1414.
von Wagner, C., Knight, K., Steptoe, A., & Wardle, J. (2007). Functional health literacy and health-promoting behaviour in a national sample of British adults. *Journal of Epidemiology and Community Health, 61*(12), 1086-1090.
von Wagner, C., Steptoe, A., Wolf, M. S., & Wardle, J. (2009). Health literacy and health actions: a review and a framework from health psychology. *Health Education & Behavior, 36*(5), 860-877.
Wallert, J., Lissåker, C., Madison, G., Held, C., & Olsson, E. (2017). Young adulthood cognitive ability predicts statin adherence in middle-aged men after first myocardial infarction: A Swedish National Registry study. *European Journal of Preventive Cardiology, 24*(6), 639-646.
Wechsler, D. (2008). *Wechsler adult intelligence scale–Fourth Edition (WAIS–IV)*. San Antonio: NCS Pearson.
Wechsler, D. (2009). *Wechsler Memory Scale–Fourth Edition (WMS–IV) technical and interpretive manual.* San Antonio, TX: Pearson.
Weiss, B. D., Mays, M. Z., Martz, W., Castro, K. M., DeWalt, D. A., Pignone, M. P., . . . Hale, F. A. (2005). Quick assessment of literacy in primary care: the newest vital sign. *Annals of Family Medicine, 3*(6), 514-522.
Williams, M. V., Baker, D. W., Honig, E. G., Lee, T. M., & Nowlan, A. (1998). Inadequate literacy is a barrier to asthma knowledge and self-care. *Chest, 114*(4), 1008-1015.
Williams, M. V., Baker, D. W., Parker, R. M., & Nurss, J. R. (1998). Relationship of functional health literacy to patients' knowledge of their chronic disease. A study of patients with hypertension and diabetes. *Archives of Internal Medicine, 158*(2), 166-172.
Wilson, R. S., Yu, L., James, B. D., Bennett, D. A., & Boyle, P. A. (2017). Association of financial and health literacy with cognitive health in old age. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition, 24*(2), 186-197.
Wolf, M. S., Davis, T. C., Arozullah, A., Penn, R., Arnold, C., Sugar, M., & Bennett, C. L. (2005). Relation between literacy and HIV treatment knowledge among patients on HAART regimens. *AIDS Care, 17*(7), 863-873.

Wolf, M. S., Gazmararian, J. A., & Baker, D. W. (2005). Health literacy and functional health status among older adults. *Archives of Internal Medicine, 165*(17), 1946-1952.
Wolf, M. S., Gazmararian, J. A., & Baker, D. W. (2007). Health literacy and health risk behaviors among older adults. *American Journal of Preventive Medicine, 32*(1), 19-24.
Wolf, M. S., Wilson, E. A., Rapp, D. N., Waite, K. R., Bocchini, M. V., Davis, T. C., & Rudd, R. E. (2009). Literacy and learning in health care. *Pediatrics, 124 Suppl 3*, S275-281.
Wolf, M. S., Curtis, L. M., Wilson, E. A., Revelle, W., Waite, K. R., Smith, S. G., . . . Baker, D. W. (2012). Literacy, cognitive function, and health: results of the LitCog study. *General Internal Medicine, 27*(10), 1300-1307.
World Health Organisation. (2013). Health Literacy: The solid facts. Copenhagen: WHO Regional Office for Europe.
Wraw, C., Deary, I. J., Gale, C. R., & Der, G. (2015). Intelligence in youth and health at age 50. *Intelligence, 53*, 23-32.
Wraw, C., Deary, I. J., Der, G., & Gale, C. R. (2016). Intelligence in youth and mental health at age 50. *Intelligence, 58*, 69-79.
Wraw, C., Der, G., Gale, C. R., & Deary, I. J. (2018). Intelligence in youth and health behaviours in middle age. *Intelligence, 69*, 71-86.
Yaffe, K., Fiocco, A. J., Lindquist, K., Vittinghoff, E., Simonsick, E. M., Newman, A. B., . . . Harris, T. B. (2009). Predictors of maintaining cognitive function in older adults: the Health ABC study. *Neurology, 72*(23), 2029-2035.
Yu, L., Wilson, R. S., Schneider, J. A., Bennett, D. A., & Boyle, P. A. (2017). Financial and Health Literacy Predict Incident Alzheimer's Disease Dementia and Pathology. *Journal of Alzheimer's Disease, 56*(4), 1485-1493.
Zhang, N. J., Terry, A., & McHorney, C. A. (2014). Impact of health literacy on medication adherence: a systematic review and meta-analysis. *Annals of Pharmacotherapy, 48*(6), 741-751.

Appendices

Appendix 1. Supplementary material for Section 5.2

Supplementary material for:

Health literacy, cognitive ability and self-reported diabetes in the English Longitudinal Study of Ageing

Supplementary Table S1. Odds ratios (95% CI) from logistic regression models of the association between health literacy and cognitive ability with whether participants self-reported a diagnosis of diabetes at wave 2 of the English Longitudinal Study of Ageing

	Model 1: Health literacy n=8,293	Model 2: Cognitive ability n=8,335	Model 3: Health literacy and cognitive ability n=8,185	Model 4: + BMI and health behaviours n=6,302	Model 5: + CV comorbidities n=6,302	Model 6: + education and social class n=6,086
Health literacy						
Limited	Reference	-	Reference	Reference	Reference	Reference
Adequate	0.72***		0.82*	0.97	1.00	0.98
	(0.61 to 0.84)		(0.69 to 0.98)	(0.78 to 1.21)	(0.81 to 1.26)	(0.78 to 1.23)
Cognitive ability	-	0.73***	0.78***	0.90	0.90	0.88
		(0.67 to 0.80)	(0.70 to 0.86)	(0.80 to 1.02)	(0.79 to 1.02)	(0.77 to 1.00)
Age	1.04***	1.03***	1.03***	1.04***	1.03***	1.03***
	(1.03 to 1.05)	(1.02 to 1.04)	(1.02 to 1.04)	(1.03 to 1.06)	(1.02 to 1.05)	(1.02 to 1.05)
Age^2	0.998***	0.998***	0.998***	0.998**	0.999*	0.999
	(0.997 to 0.999)	(0.997 to 0.998)	(0.997 to 0.999)	(0.997 to 0.999)	(0.998 to 1.000)	(0.998 to 1.000)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.50***	1.41***	1.43***	2.16***	2.13***	2.09***
	(1.28 to 1.77)	(1.20 to 1.66)	(1.22 to 1.69)	(1.75 to 2.68)	(1.72 to 2.65)	(1.67 to 2.62)
BMI				1.10***	1.09***	1.09***
				(1.08 to 1.12)	(1.07 to 1.11)	(1.07 to 1.11)
Current smoking						
Non-smoker				Reference	Reference	Reference
Smoker				0.91	0.93	0.93
				(0.66 to 1.24)	(0.68 to 1.27)	(0.66 to 1.27)
Alcohol consumption						
Daily/almost daily				Reference	Reference	Reference
At least once per week				1.21	1.22	1.24
				(0.90 to 1.65)	(0.90 to 1.66)	(0.91 to 1.70)
At least once per month				1.78**	1.76**	1.77**
				(1.24 to 2.56)	(1.22 to 2.54)	(1.21 to 2.57)
Rarely				1.95***	1.87***	1.95***

	(1.38 to 2.76)	(1.32 to 2.66)	(1.36 to 2.79)
Never	2.40***	2.26***	2.12***
	(1.67 to 3.44)	(1.57 to 3.25)	(1.45 to 3.11)
Physical activity			
Inactive	Reference	Reference	Reference
Moderate activity	0.65***	0.70**	0.68**
	(0.51 to 0.83)	(0.55 to 0.88)	(0.53 to 0.87)
Vigorous activity	0.50***	0.57***	0.56***
	(0.37 to 0.68)	(0.42 to 0.77)	(0.41 to 0.76)
Number of CV comorbidities		1.94***	1.98***
		(1.67 to 2.26)	(1.70 to 2.32)
Number of CV comorbidities^2		0.89***	0.88***
		(0.83 to 0.94)	(0.82 to 0.93)
Age left full-time education			
14 years or under			Reference
15-16 years			1.17
			(0.87 to 1.56)
17-18 years			0.98
			(0.64 to 1.50)
19 years or older			1.32
			(0.85 to 2.05)
Social class			
Managerial and professional			Reference
Intermediate			0.79
			(0.58 to 1.07)
Routine and manual			1.01
			(0.77 to 1.32)

*p < .05, **p < .01, ***p < .001

Age^2, age squared; BMI, body mass index; CV, cardiovascular; number of CV cormorbidities^2, number of cardiovascular comorbidities squared.

Supplementary Table S2. Hazard ratios (95% CI) from Cox regression models of the association between health literacy and cognitive ability with risk of incident diabetes

	Model 1: Health literacy n=6,736 Events=490	Model 2: Cognitive ability n=6,746 Events=491	Model 3: Health literacy and cognitive ability n=6,654 Events=484	Model 4: + BMI health behaviours n=5,357 Events=377	Model 5: + CV comorbidities n=5,357 Events=377	Model 6: + education and social class n=5,186 Events=360
Health literacy						
Limited	Reference	-	Reference	Reference	Reference	Reference
Adequate	0.64***		0.72***	0.79*	0.80*	0.85
	(0.53 to 0.77)		(0.59 to 0.87)	(0.64 to 0.99)	(0.64 to 0.99)	(0.68 to 1.06)
Cognitive ability	-	0.77***	0.79***	0.85*	0.85*	0.88
		(0.69 to 0.85)	(0.71 to 0.88)	(0.74 to 0.96)	(0.74 to 0.96)	(0.77 to 1.01)
Age	1.01	1.00	1.00	1.01	1.01	1.01
	(1.00 to 1.02)	(0.99 to 1.01)	(0.98 to 1.01)	(1.00 to 1.02)	(0.99 to 1.02)	(0.99 to 1.02)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.43***	1.39***	1.38***	1.84***	1.83***	1.82***
	(1.20 to 1.71)	(1.16 to 1.66)	(1.15 to 1.65)	(1.49 to 2.29)	(1.48 to 2.27)	(1.45 to 2.28)
BMI				1.12***	1.12***	1.12***
				(1.10 to 1.14)	(1.10 to 1.14)	(1.10 to 1.13)
Current smoking						
Non-smoker				Reference	Reference	Reference
Smoker				1.77***	1.77***	1.69***
				(1.35 to 2.31)	(1.36 to 2.31)	(1.28 to 2.22)
Alcohol consumption						
Daily/almost daily				Reference	Reference	Reference
At least once per week				1.11	1.123	1.01
				(0.83 to 1.49)	(0.84 to 1.51)	(0.75 to 1.37)
At least once per month				1.53*	1.54*	1.40
				(1.07 to 2.19)	(1.08 to 2.20)	(0.97 to 2.01)
Rarely				1.78***	1.78***	1.53*
				(1.27 to 2.50)	(1.27 to 2.50)	(1.08 to 2.17)
Never				1.42	1.39	1.15

	(0.95 to 2.11)	(0.93 to 2.07)	(0.76 to 1.73)
Physical activity			
Inactive	Reference	Reference	Reference
Moderate activity	0.78 (0.61 to 1.01)	0.80 (0.62 to 1.03)	0.79 (0.61 to 1.03)
Vigorous activity	0.72* (0.54 to 0.98)	0.75 (0.56 to 1.01)	0.76 (0.56 to 1.04)
Number of CV comorbidities		1.18** (1.06 to 1.31)	1.17** (1.05 to 1.30)
Age left full-time education			
14 years or under			Reference
15-16 years			1.00 (0.74 to 1.36)
17-18 years			0.73 (0.47 to 1.15)
19 years or older			0.58* (0.35 to 0.96)
Social class			
Managerial and professional			Reference
Intermediate			0.91 (0.66 to 1.24)
Routine and manual			1.17 (0.89 to 1.53)

$*p < .05$, $**p < .01$, $***p < .001$
BMI, body mass index; CV, cardiovascular.

Supplementary Table S3. Odds ratios (95% CI) for the association between health literacy and cognitive ability with cross-sectional diabetes status at wave 2 of the English Longitudinal Study of Ageing. Models are run on a sub-sample of 6,086 participants with data on all variables of interest.

	Model 1: Health literacy	Model 2: Cognitive ability	Model 3: Health literacy and cognitive ability	Model 4: + BMI and health behaviours	Model 5: + CV comorbidities	Model 6: + education and social class
Health literacy						
Limited	Reference	-	Reference	Reference	Reference	Reference
Adequate	0.79*		0.88	0.96	0.99	0.98
	(0.64 to 0.97)		(0.71 to 1.10)	(0.77 to 1.20)	(0.79 to 1.24)	(0.78 to 1.23)
Cognitive ability	-	0.78***	0.79***	0.88	0.88*	0.88
		(0.69 to 0.88)	(0.70 to 0.90)	(0.77 to 1.00)	(0.77 to 1.00)	(0.77 to 1.00)
Age	1.04***	1.03***	1.03***	1.04***	1.03***	1.03***
	(1.03 to 1.06)	(1.02 to 1.05)	(1.02 to 1.05)	(1.02 to 1.05)	(1.01 to 1.04)	(1.02 to 1.05)
Age^2	0.999*	0.999**	0.999**	0.998**	0.999	0.999
	(0.997 to 1.000)	(0.997 to 1.000)	(0.997 to 1.000)	(0.997 to 1.000)	(0.998 to 1.000)	(0.998 to 1.000)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.66***	1.58***	1.58***	2.17***	2.14***	2.09***
	(1.36 to 2.03)	(1.29 to 1.93)	(1.29 to 1.94)	(1.74 to 2.70)	(1.72 to 2.68)	(1.67 to 2.62)
BMI				1.10***	1.09***	1.09***
				(1.08 to 1.12)	(1.07 to 1.11)	(1.07 to 1.11)
Current smoking						
Non-smoker				Reference	Reference	Reference
Smoker				0.89	0.92	0.93
				(0.64 to 1.22)	(0.66 to 1.26)	(0.66 to 1.27)
Alcohol consumption						
Daily/almost daily				Reference	Reference	Reference
At least once per week				1.22	1.22	1.24
				(0.90 to 1.66)	(0.90 to 1.67)	(0.91 to 1.70)
At least once per month				1.76**	1.73**	1.77**
				(1.21 to 2.54)	(1.19 to 2.52)	(1.21 to 2.57)

Rarely		2.01*** (1.42 to 2.87)	1.94*** (1.36 to 2.77)	1.95*** (1.36 to 2.79)
Never		2.25*** (1.55 to 3.26)	2.10*** (1.44 to 3.06)	2.12*** (1.45 to 3.11)
Physical activity				
Inactive		Reference	Reference	Reference
Moderate activity		0.65*** (0.51 to 0.82)	0.69** (0.54 to 0.88)	0.68** (0.53 to 0.87)
Vigorous activity		0.51*** (0.37 to 0.69)	0.56*** (0.41 to 0.77)	0.56*** (0.41 to 0.76)
Number of CV comorbidities			1.98*** (1.70 to 2.32)	1.98*** (1.70 to 2.32)
Number of CV comorbidities^2			0.87*** (0.82 to 0.93)	0.88*** (0.82 to 0.93)
Education				
14 years or under				Reference
15-16 years				1.17 (0.87 to 1.56)
17-18 years				0.98 (0.64 to 1.50)
19 years or older				1.32 (0.85 to 2.05)
Social class				
Managerial and professional				Reference
Intermediate				0.79 (0.58 to 1.07)
Routine and manual				1.01 (0.77 to 1.32)

*p < .05, **p < .01, ***p < .001

Age^2, age squared; BMI, body mass index; CV, cardiovascular; number of CV cormorbidities^2, number of cardiovascular comorbidities squared.

Supplementary Table S4. Hazard ratios (95% CIs) from Cox regression models of the association between health literacy and cognitive ability with risk of incident diabetes. Models are run on a sub-sample of 5,186 (360 with incident diabetes) participants with data on all variables of interest.

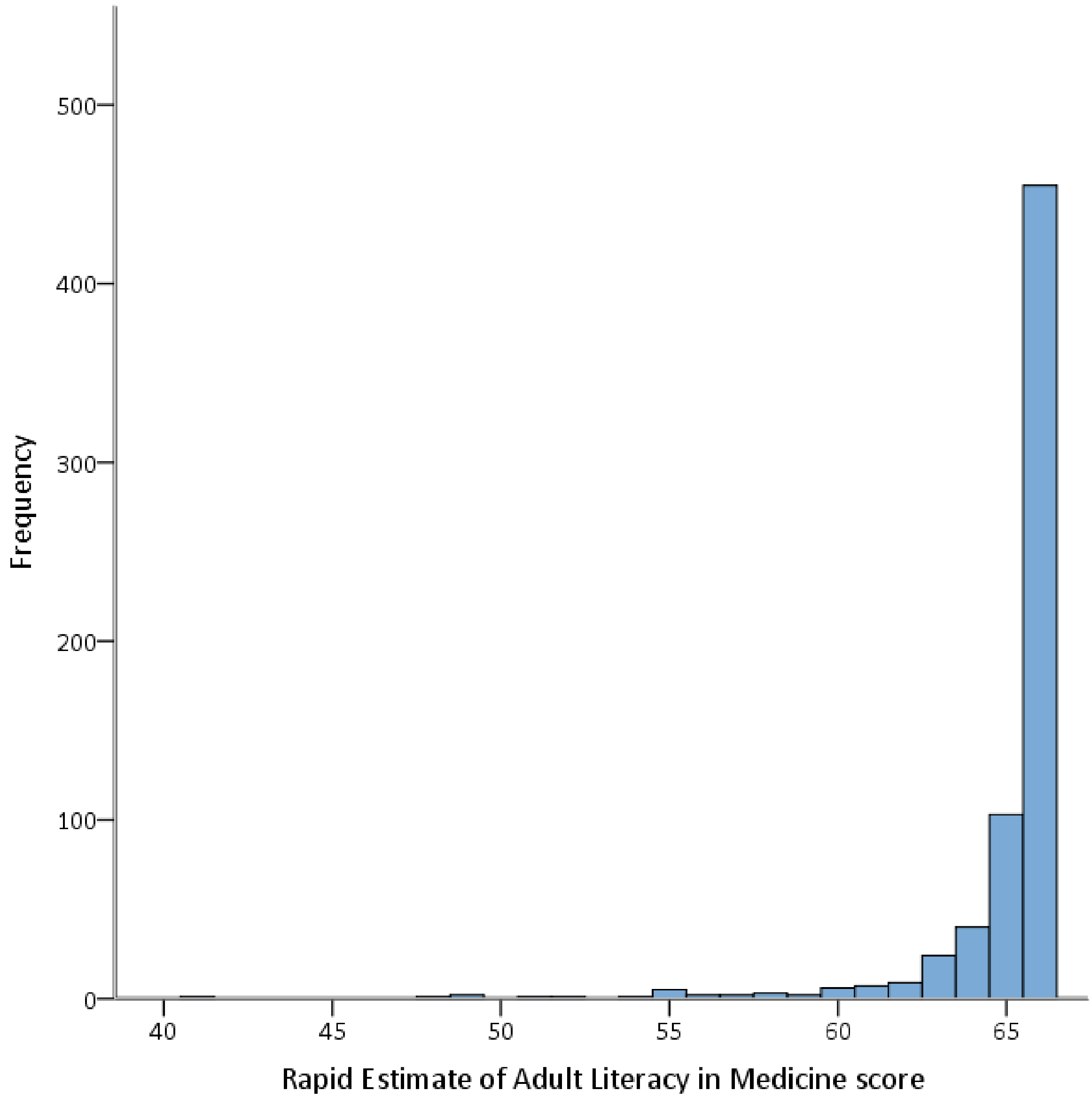
	Model 1: Health literacy	Model 2: Cognitive ability	Model 3: Health literacy and cognitive ability	Model 4: + BMI and health behaviours	Model 5: + CV comorbidities	Model 6: + education and social class
Health literacy						
Limited	Reference	-	Reference	Reference	Reference	Reference
Adequate	0.64***		0.73**	0.80	0.81	0.85
	(0.52 to 0.80)		(0.58 to 0.91)	(0.64 to 1.01)	(0.65 to 1.02)	(0.68 to 1.06)
Cognitive ability	-	0.72***	0.76***	0.84**	0.84**	0.88
		(0.63 to 0.82)	(0.66 to 0.86)	(0.73 to 0.96)	(0.73 to 0.96)	(0.77 to 1.01)
Age	1.01	1.00	1.00	1.01	1.01	1.01
	(0.997 to 1.02)	(0.98 to 1.01)	(0.98 to 1.01)	(0.997 to 1.03)	(0.99 to 1.02)	(0.99 to 1.02)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.47***	1.38**	1.40**	1.82***	1.80***	1.82***
	(1.20 to 1.81)	(1.12 to 1.70)	(1.13 to 1.72)	(1.46 to 2.27)	(1.45 to 2.25)	(1.45 to 2.28)
BMI				1.12***	1.12***	1.12***
				(1.10 to 1.14)	(1.10 to 1.14)	(1.10 to 1.13)
Current smoking						
Non-smoker				Reference	Reference	Reference
Smoker				1.79***	1.79***	1.70***
				(1.36 to 2.34)	(1.36 to 2.35)	(1.28 to 2.22)
Alcohol consumption						
Daily/almost daily				Reference	Reference	Reference
At least once per week				1.10	1.09	1.01
				(0.80 to 1.46)	(0.81 to 1.47)	(0.75 to 1.37)
At least once per month				1.49*	1.49*	1.40
				(1.03 to 2.14)	(1.04 to 2.15)	(0.97 to 2.01)
Rarely				1.70**	1.70**	1.53*
				(1.20 to 2.40)	(1.20 to 2.40)	(1.08 to 2.17)

Never	1.30 (0.86 to 1.96)	1.27 (0.85 to 1.92)	1.15 (0.76 to 1.73)
Physical activity			
Inactive	Reference	Reference	Reference
Moderate activity	0.76* (0.59 to 0.99)	0.78 (0.60 to 1.01)	0.79 (0.61 to 1.03)
Vigorous activity	0.71* (0.52 to 0.96)	0.73* (0.54 to 0.995)	0.76 (0.56 to 1.04)
Number of CV comorbidities		1.17** (1.06 to 1.30)	1.17** (1.05 to 1.30)
Education			
14 years or under			Reference
15-16 years			1.00 (0.74 to 1.36)
17-18 years			0.73 (0.47 to 1.15)
19 years or older			0.58* (0.35 to 0.96)
Social class			
Managerial and professional			Reference
Intermediate			0.91 (0.66 to 1.24)
Routine and manual			1.17 (0.89 to 1.53)

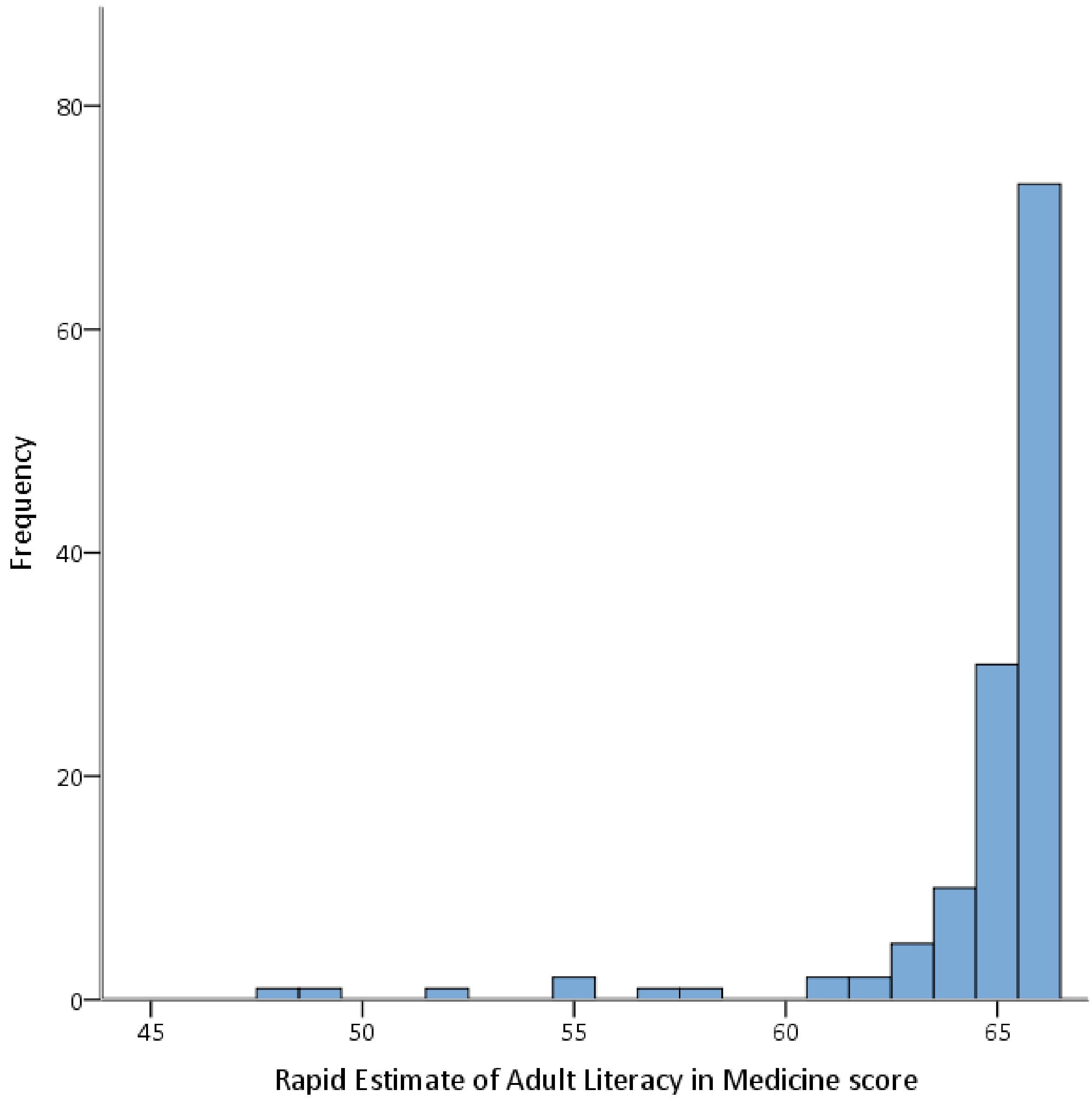
*$p < .05$, **$p < .01$, ***$p < .001$
BMI, body mass index; CV, cardiovascular.

Appendix 2. Supplementary material for Section 6.2

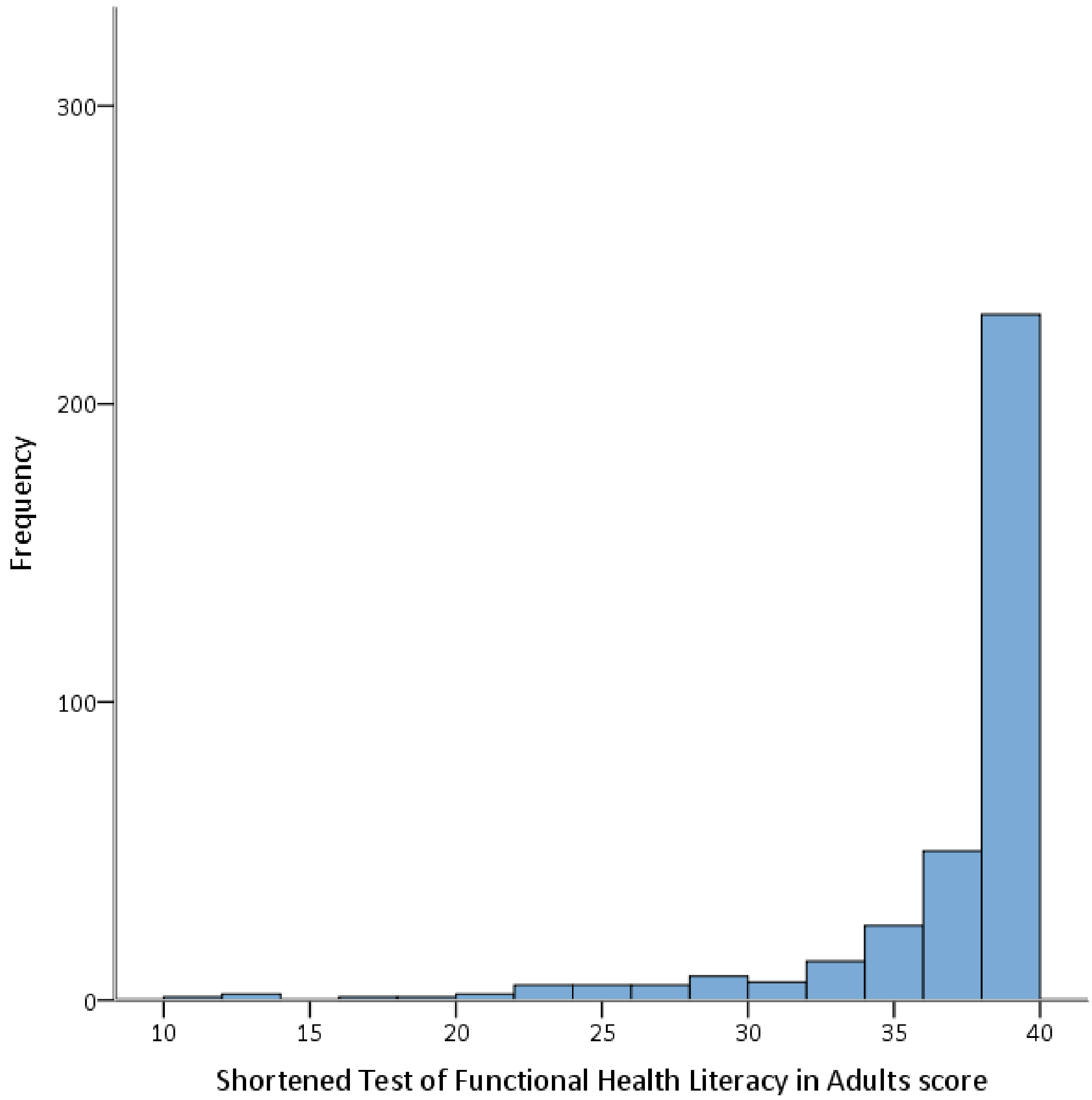
Supplementary material for: The role of cognitive ability in the association between functional health literacy and mortality in the Lothian Birth Cohort 1936: a prospective cohort study



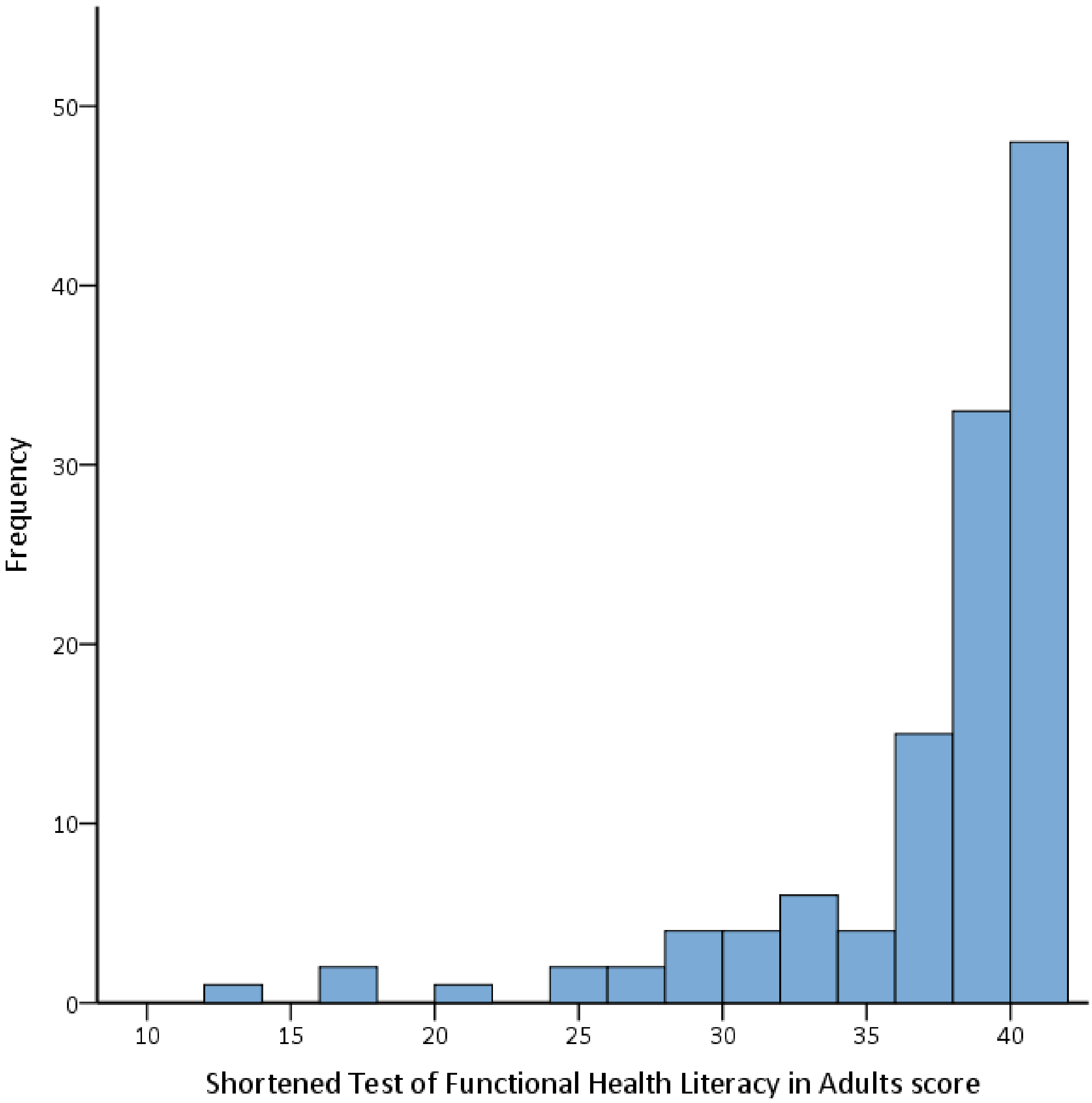
Supplementary Figure 1 Distribution of scores on the Rapid Estimate of Adult Literacy in Medicine for participants who were alive at censoring date.



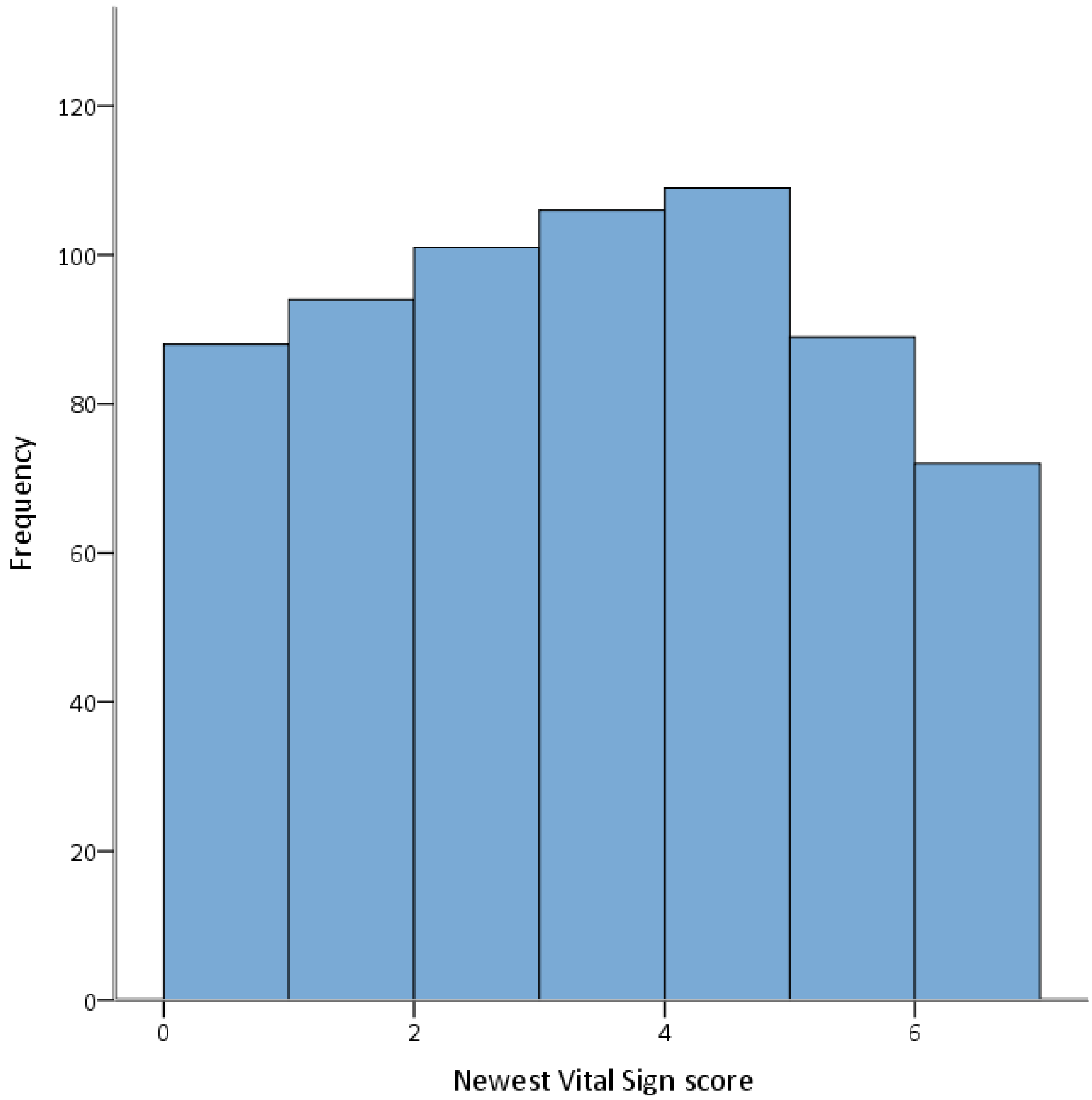
Supplementary Figure 2 Distribution of scores on the Rapid Estimate of Adult Literacy in Medicine for participants who had died by censoring date.



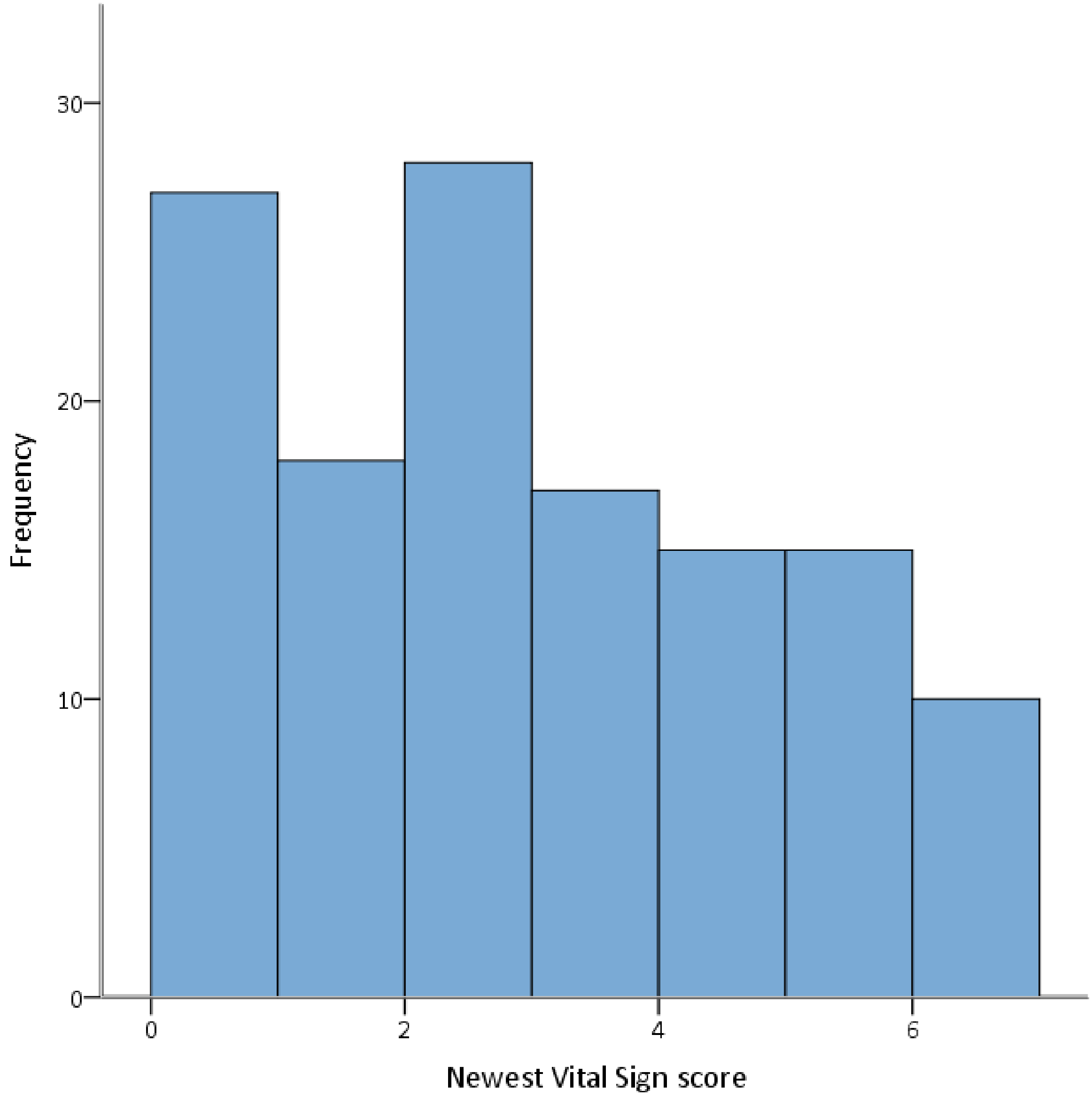
Supplementary Figure 3 Distribution of scores on the Shortened Test of Functional Health Literacy in Adults for participants who were alive at censoring date.



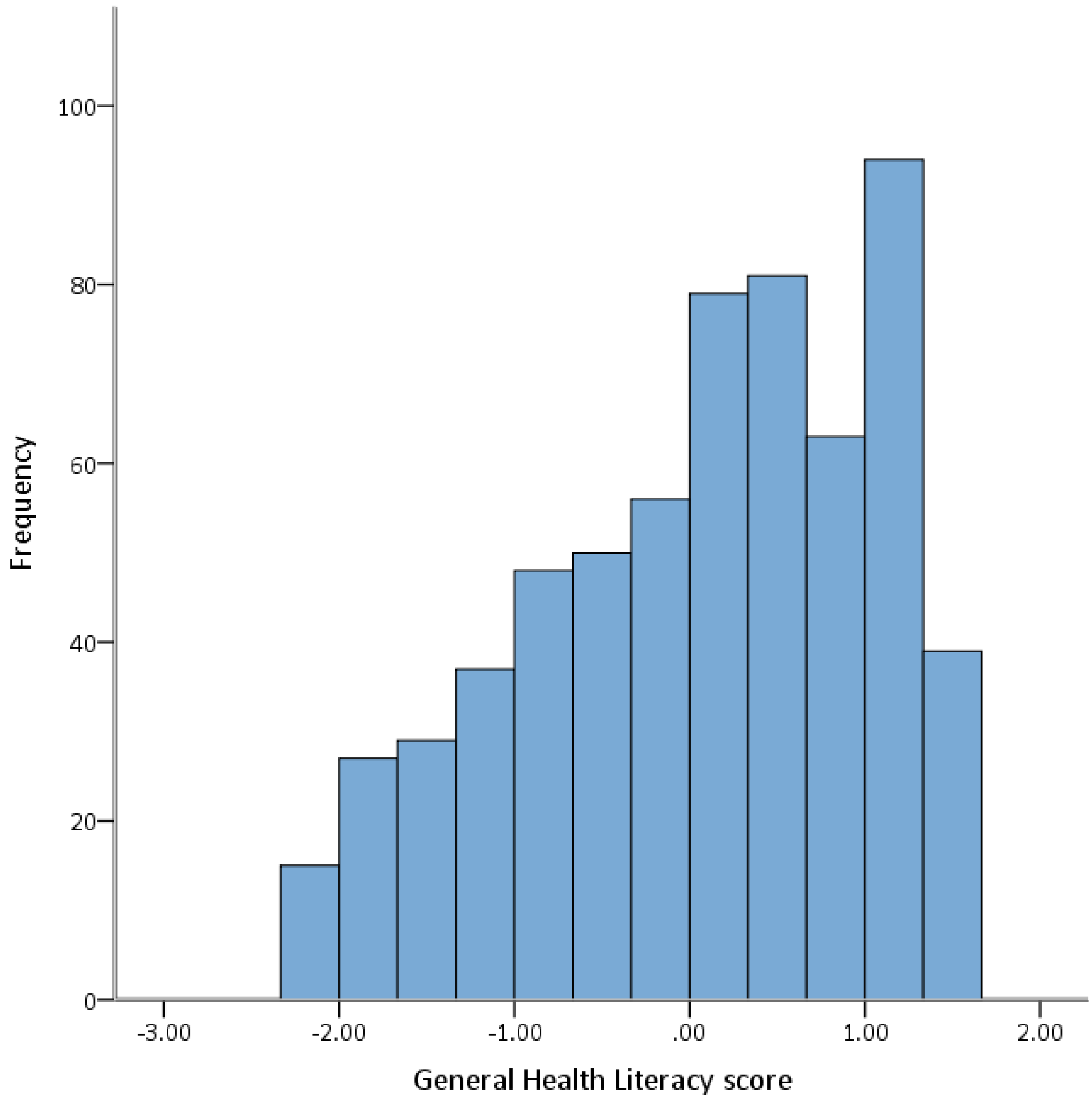
Supplementary Figure 4 Distribution of scores on the Shortened Test of Functional Health Literacy in Adults for participants who has died by censoring date.



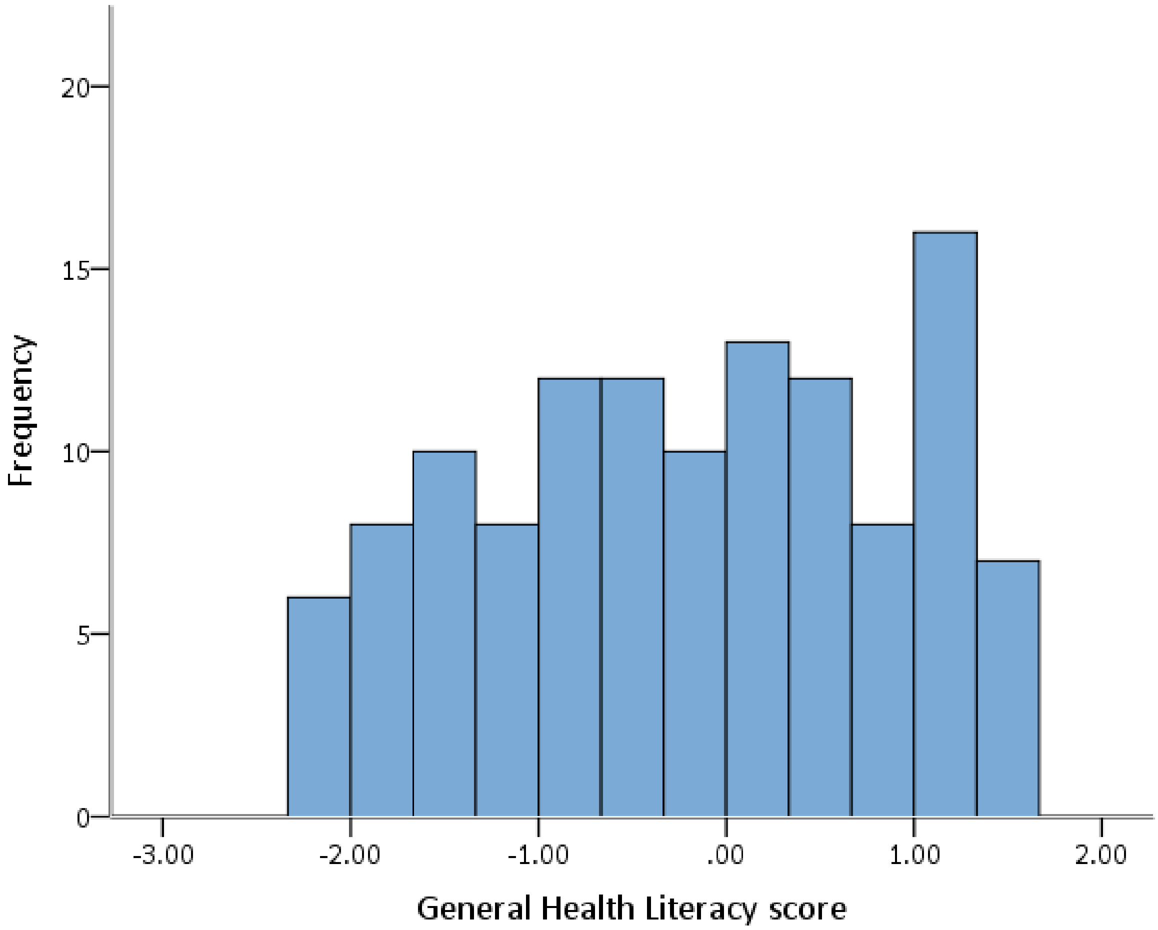
Supplementary Figure 5 Distribution of scores on the Newest Vital Sign for participants who were alive at censoring date.



Supplementary Figure 6 Distribution of scores on the Newest Vital Sign for participants who had died by censoring date.



Supplementary Figure 7 Distribution of scores on General Health Literacy for participants who were alive at censoring date.



Supplementary Figure 8 Distribution of scores on General Health Literacy for participants who had died by censoring date.

Supplementary Table 1 Rank order correlations between sociodemographic, functional health literacy, cognitive and health variables

	1	2	3	4	5	6	7	8	9	10	11	12	13
1 Age	-												
2 Sex†	0.04	-											
3 REALM	-0.12**	0.17***	-										
4 S-TOFHLA	-0.05	0.10**	0.40***	-									
5 NVS	-0.12**	0.01	0.35***	0.44***	-								
6 General functional health literacy	-0.09*	0.14***	0.71***	0.80***	0.78***	-							
7 Age-11 IQ	-0.07*	0.11**	0.44***	0.48***	0.51***	0.61***	-						
8 Fluid ability	-0.13***	0.00	0.38***	0.55***	0.55***	0.63***	0.57***	-					
9 Education	-0.05	0.03	0.31***	0.33***	0.37***	0.45***	0.45***	0.37***	-				
10 Occup class	0.05	-0.15***	-0.31***	-0.31***	-0.32***	-0.39***	-0.40***	-0.35***	-0.47***	-			
11 Self-rated health	-0.02	0.06	0.12**	0.20***	0.11**	0.18***	0.17***	0.24***	0.11**	-0.11**	-		
12 HADS	0.06	0.08*	-0.07	-0.13**	-0.11**	-0.14***	-0.13***	-0.22***	-0.08*	0.08*	-0.32***	-	
13 Townsend	0.13***	0.16***	-0.08*	-0.12**	-0.15***	-0.14***	-0.12**	-0.17***	-0.12**	0.09*	-0.35***	0.22***	-

*$p < .05$, **$p < .01$, ***$p < .001$.

†Correlations are point-biseral correlations. Female is coded 1 and male is coded 2.

Occupational class (ranging from 1-professional to 4-manual) and self-rated health (ranging from 1-poor/fair to 3-very good/excellent) are entered as ordinal variables.

REALM, Rapid Estimate of Adult Literacy in Medicine; S-TOFHLA, Shortened Test of Functional Health Literacy in Adults; NVS, Newest Vital Sign; IQ, Intelligence Quotient; Occup class, occupational class; HADS, Hospital Anxiety and Depression Scale; Townsend, Townsend Disability Scale.

DETAILED RESULTS

REALM: Hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between the REALM and mortality are shown in Supplementary Table 2. In Model 1, in which age and sex were controlled, the REALM did not significantly predict mortality (HR = 0.954, 95% CI 0.904 to 1.007), nor did age or sex. The REALM remained a non-significant predictor of mortality in Model 2, with the addition of years of education. Years of education did not predict mortality (HR = 0.963, 95% CI 0.822 to 1.128). Age-11 IQ was added in Model 3, and this did little to change the association between the REALM and mortality. Age-11 IQ did not predict mortality (HR = 0.993, 95% CI 0.980 to 1.006). The REALM remained a non-significant predictor of mortality following the inclusion of current fluid ability in Model 4. A one SD increase in fluid ability score reduced the risk of death by 37.9% (HR = 0.621, 95% CI 0.496 to 0.777). In Model 5, occupational social class was included in the model. The REALM remained non-significant. Individuals with a managerial/technical social class (HR = 2.278, 95% CI 1.161 to 4.470), a skilled non-manual social class (HR = 2.464, 95% CI 1.167 to 5.201) or a skilled manual social class (HR = 3.608, 95% CI 1.647 to 7.907) had a higher risk of death than individuals with a professional social class. Health status variables were additionally added in Model 6. The REALM remained a non-significant predictor of mortality. In this model, individuals with more years of education had a higher risk of dying (HR = 1.232, 95% CI 1.018 to 1.492). Risk of death for those who self-reported their health as fair or poor was over 2 times greater than those who reported their health to be very good or excellent (HR = 2.071, 95% CI 1.147 to 3.739). While HADS score did not predict mortality, Townsend disability did. A one-point increase on the Townsend disability scale increased risk of mortality by 13.3% (HR = 1.133, 95% CI 1.044 to 1.229).

S-TOFHLA: The HRs for the association between S-TOFHLA and mortality are shown in Supplementary Table 3. In Model 1, controlling for age and sex, S-TOFHLA significantly predicted mortality. A one-point increase in S-TOFHLA reduced the risk of death by 5.2% (HR = 0.948, 95% CI 0.919 to 0.978). In this model, age and sex did not predict mortality. Adding years of education in Model 2 did not change the association between the S-TOFHLA and mortality. Years of education did not predict mortality (HR = 1.020, 95% CI 0.870 to 1.197). The inclusion of age-11 IQ in Model 3 did not change the association between the S-TOFHLA and mortality. Age-11 IQ also did not predict mortality (HR = 0.997, 95% CI 0.983 to 1.011). The association between the S-TOFHLA and mortality was attenuated and became non-significant (HR = 0.967, 95% CI 0.929 to 1.007) in Model 4, additionally accounting current fluid ability. Current fluid ability significantly predicted mortality in this model. A one SD increase in fluid ability reduced the risk of death by 30.5% (HR = 0.695, 95% CI 0.545 to 0.887). Occupational class was included in Model 5, and the association between S-TOFHLA and mortality remained non-significant. Individuals with more years of education, controlling for other sociodemographic variables and cognitive function, had increased risk of death (HR = 1.219, 95% CI 1.004 to 1.481). Risk of dying was three times greater for participants with a skilled manual social class, compared to individuals with a professional social class (HR = 3.096, 95% CI 1.385 to 6.922). S-TOFHLA remained a non-significant predictor or mortality in Model 6, which included health status variables. Self-reporting health as fair or poor, compared to very good or excellent, was associated with increased risk of mortality (HR = 2.209, 95% CI 1.216 to 4.014). Higher scores on the HADS were not associated with mortality, while a higher Townsend disability score increased risk of death (HR = 1.131, 95% CI 1.039 to 1.232).

NVS: HRs for the association between NVS and mortality are shown in Supplementary Table 4. In Model 1, in which age and sex were entered as covariates, NVS significantly predicted mortality. A one point increase in NVS score reduced the risk of death by 11.8% (HR = 0.882, 95% CI 0.805 to 0.966). Age and sex did not predict mortality. Years of education was included in Model 2 and this did not change the association between the NVS and mortality. Years of education did not predict mortality (HR = 1.007, 95% CI 0.855 to 1.186). Age-11 IQ was additionally added to the model in Model 3 and this did little to change the association between NVS and mortality and this association remained significant. Age-11 IQ did not predict mortality (HR = 0.995, 95% CI 0.982 to 1.008). The inclusion of fluid ability in Model 4 greatly attenuated the association between NVS and mortality, and this became non-significant (HR = 0.963, 95% CI 0.860 to 1.078). Fluid ability was strongly associated with risk of death. A one SD increase in fluid ability score reduced risk of dying by 37.0% (HR = 0.630, 95% CI 0.496 to 0.800). The association between NVS and mortality remained non-significant in Model 5 following inclusion of occupational class in the model. Compared to those with a professional social class, participants with managerial or technical (HR = 2.288, 95% CI 1.166 to 4.490), skilled non-manual (HR = 2.421, 95% CI 1.147 to 5.112), and skilled manual (HR = 3.631, 95% CI 1.658 to 7.951) social class had an increased risk of death. Finally, health status variables were included in Model 6. The inclusion of health status variables did little to change the association between NVS and mortality, which remained non-significant. In this model, having more years of education was associated with increased risk of mortality (HR = 1.242, 95% CI 1.023 to 1.508). Those who reported their health as fair or poor had 2.10 times (HR = 2.099, 95% CI 1.167 to 3.775) increased risk of mortality, compared to those who self-reported their health as very good or excellent. Participants with higher scores on the Townsend disability scale also had an increased risk of mortality (HR = 1.132, 95% CI 1.044 to 1.228).

General functional health literacy: HRs for the association between general functional health literacy and mortality are shown in Supplementary Table 5. General functional health literacy predicted mortality in Model 1 (HR = 0.774, 95% CI 0.650 to 0.922), while age and sex did not. A one point increase in the general functional health literacy score reduced the risk of mortality by 22.6%. Adding years of education (Model 2) did little to change the association between general functional health literacy and mortality and this association remained significant. Years of education was not associated with mortality (HR = 1.080, 95% CI 0.909 to 1.284). General functional health literacy remained a significant predictor of mortality when age-11 IQ was added in Model 3. Age-11 IQ did not predict morality (HR = 0.999, 95% CI 0.984 to 1.014). The inclusion of current fluid ability in Model 4 attenuated the association between general functional health literacy and risk of death, and this association became non-significant (HR = 0.871, 95% CI 0.674 to 1.125). Fluid ability was a significant predictor of mortality, such that a one SD increase in fluid ability reduced risk of death by 31.3% (HR = 0.687, 95% CI 0.531 to 0.887). Including occupational social class in Model 5 did little to change the association between general functional health literacy and mortality, and this association remained non-significant. In Model 4, individuals with more years of education had a greater risk of death (HR = 1.240, 95% CI 1.019 to 1.508), and those with an occupational social class of skilled manual (HR = 3.134, 95% CI 1.405 to 6.991), when compared to those with a professional occupational class, had an increased risk of mortality. Finally, health status variables were added in Model 6. The association between general functional health literacy and mortality was attenuated further and remained non-significant. Reporting fair or poor health, compared to reporting very good or excellent health increased the risk of mortality (HR = 2.229, 95% CI 1.229 to 4.042). Higher Townsend disability scores were also associated with increased risk of death (HR = 1.128, 95% CI 1.040 to 1.225). In this final model, controlling for sociodemographics and health variables, as well as age-11 IQ, the association between fluid ability and mortality was attenuated and became non-significant (HR = 0.770, 95% CI 0.589 to 1.007).

Supplementary Table 2 Hazard ratios (95% confidence intervals) for the association between REALM and mortality, controlling for sociodemographic, cognitive ability, and health status variables

	Model 1 Age and sex N = 794	Model 2 + education N = 794	Model 3 + age-11 IQ N = 752	Model 4 + current fluid ability N = 746	Model 5 + occup class N = 731	Model 6 + health status N = 728
REALM	0.954 (0.904 to 1.007)	0.957 (0.905 to 1.013)	0.962 (0.903 to 1.025)	0.971 (0.907 to 1.039)	0.970 (0.904 to 1.040)	0.996 (0.924 to 1.074)
Age	0.940 (0.725 to 1.219)	0.939 (0.724 to 1.218)	0.944 (0.725 to 1.231)	0.879 (0.669 to 1.154)	0.908 (0.686 to 1.203)	0.933 (0.704 to 1.235)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.297 (0.909 to 1.850)	1.298 (0.910 to 1.852)	1.252 (0.869 to 1.802)	1.333 (0.927 to 1.918)	1.176 (0.787 to 1.756)	1.364 (0.898 to 2.073)
Years of education		0.963 (0.822 to 1.128)	1.022 (0.862 to 1.211)	1.089 (0.916 to 1.295)	1.201 (0.995 to 1.450)	1.232 (1.018 to 1.492)*
Age-11 IQ			0.993 (0.980 to 1.006)	1.008 (0.993 to 1.023)	1.009 (0.994 to 1.024)	1.008 (0.993 to 1.024)
Fluid ability				0.621 (0.496 to 0.777)***	0.662 (0.526 to 0.834)***	0.727 (0.574 to 0.922)**
Occupational class						
Professional					Reference	Reference
Managerial/technical					2.278 (1.161 to 4.470)*	2.218 (1.127 to 4.365)*
Skilled: non-manual					2.464 (1.167 to 5.201)*	2.596 (1.232 to 5.474)*
Skilled: manual					3.608 (1.647 to 7.907)**	3.393 (1.532 to 7.516)**
Partly skilled/ unskilled manual					2.054 (0.651 to 6.473)	2.067 (0.656 to 6.510)
Self-rated health						
Very good/excellent						Reference
Good						1.153 (0.742 to 1.791)
Fair/poor						2.071 (1.147 to 3.739)*
HADS total score						0.972 (0.929 to 1.018)
Townsend disability						1.133 (1.044 to 1.229)**

* $p < .05$, ** $p < .01$, *** $p < .001$.

REALM, Rapid Estimate of Adult Literacy in Medicine; IQ, Intelligence Quotient; occup class, Occupational class; HADS, Hospital Anxiety and Depression Scale.

Supplementary Table 3 Hazard ratios (95% confidence intervals) for the association between S-TOFHLA and mortality, controlling for sociodemographic, cognitive ability, and health variables

	Model 1 Age and sex N = 744	Model 2 + education N = 744	Model 3 + age-11 IQ N = 702	Model 4 + current fluid ability N = 697	Model 5 + occup class N = 682	Model 6 + health status N = 680
S-TOFHLA	0.948 (0.919 to 0.978)**	0.947 (0.917 to 0.978)**	0.947 (0.913 to 0.982)**	0.967 (0.929 to 1.007)	0.976 (0.935 to 1.019)	0.998 (0.953 to 1.046)
Age	0.882 (0.665 to 1.170)	0.882 (0.665 to 1.170)	0.889 (0.666 to 1.186)	0.871 (0.652 to 1.164)	0.919 (0.682 to 1.238)	0.936 (0.697 to 1.256)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.307 (0.909 to 1.879)	1.309 (0.910 to 1.881)	1.277 (0.881 to 1.851)	1.349 (0.930 to 1.956)	1.204 (0.797 to 1.818)	1.352 (0.881 to 2.074)
Years of education		1.020 (0.870 to 1.197)	1.066 (0.896 to 1.268)	1.111 (0.932 to 1.326)	1.219 (1.004 to 1.481)*	1.249 (1.026 to 1.520)*
Age-11 IQ			0.997 (0.983 to 1.011)	1.006 (0.991 to 1.022)	1.007 (0.991 to 1.022)	1.006 (0.991 to 1.022)
Fluid ability				0.695 (0.545 to 0.887)**	0.717 (0.557 to 0.922)*	0.759 (0.587 to 0.982)*
Occupational class						
Professional					Reference	Reference
Managerial/technical					1.889 (0.956 to 3.734)	1.844 (0.931 to 3.650)
Skilled: non-manual					2.108 (0.994 to 4.470)	2.207 (1.042 to 4.673)*
Skilled: manual					3.096 (1.385 to 6.922)**	2.881 (1.275 to 6.509)*
Partly skilled/ unskilled manual					1.786 (0.566 to 5.636)	1.773 (0.562 to 5.598)
Self-rated health						
Very good/excellent						Reference
Good						1.147 (0.728 to 1.807)
Fair/poor						2.209 (1.216 to 4.014)**
HADS total score						0.974 (0.930 to 1.021)
Townsend disability						1.131 (1.039 to 1.232)**

**p* < .05, ***p* < .01, ****p* < .001.

S-TOFHLA, Shortened Test of Functional Health Literacy in Adults; IQ, Intelligence Quotient; occup class, Occupational class; HADS, Hospital Anxiety and Depression Scale.

Supplementary Table 4 Hazard ratios (95% confidence intervals) for the association between NVS and mortality, controlling for sociodemographic, cognitive ability, and health variables

	Model 1 Age and sex N = 789	Model 2 + education N = 789	Model 3 + age-11 IQ N = 746	Model 4 + current fluid ability N = 742	Model 5 + occup class N = 727	Model 6 + health status N = 724
NVS	0.882 (0.805 to 0.966)**	0.880 (0.799 to 0.970)*	0.892 (0.802 to 0.992)*	0.963 (0.860 to 1.078)	0.967 (0.861 to 1.086)	0.961 (0.853 to 1.082)
Age	0.942 (0.727 to 1.221)	0.942 (0.726 to 1.221)	0.942 (0.722 to 1.228)	0.890 (0.678 to 1.168)	0.919 (0.694 to 1.217)	0.937 (0.708 to 1.242)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.343 (0.946 to 1.906)	1.343 (0.947 to 1.907)	1.279 (0.892 to 1.834)	1.346 (0.939 to 1.928)	1.180 (0.791 to 1.760)	1.355 (0.893 to 2.057)
Years of education		1.007 (0.855 to 1.186)	1.056 (0.888 to 1.257)	1.093 (0.917 to 1.302)	1.208 (0.998 to 1.463)	1.242 (1.023 to 1.508)*
Age-11 IQ			0.995 (0.982 to 1.008)	1.007 (0.993 to 1.021)	1.008 (0.993 to 1.023)	1.009 (0.994 to 1.023)
Fluid ability				0.630 (0.496 to 0.800)***	0.670 (0.524 to 0.857)**	0.748 (0.580 to 0.966)*
Occupational class						
Professional					Reference	Reference
Managerial/technical					2.288 (1.166 to 4.490)*	2.243 (1.140 to 4.414)*
Skilled: non-manual					2.421 (1.147 to 5.112)*	2.593 (1.231 to 5.463)*
Skilled: manual					3.631 (1.658 to 7.951)**	3.360 (1.522 to 7.415) **
Partly skilled/ unskilled manual					2.125 (0.677 to 6.669)	2.086 (0.661 to 6.578)
Self-rated health						
Very good/excellent						Reference
Good						1.175 (0.756 to 1.826)
Fair/poor						2.099 (1.167 to 3.775)*
HADS total score						0.973 (0.930 to 1.018)
Townsend disability						1.132 (1.044 to 1.228)**

*$p < .05$, **$p < .01$.

NVS, Newest Vital Sign; IQ, Intelligence Quotient; occup class, Occupational class; HADS, Hospital Anxiety and Depression Scale.

Supplementary Table 5 Hazard ratios (95% confidence intervals) for the association between general functional health literacy and mortality, controlling for sociodemographic, cognitive ability, and health variables

	Model 1 Age and sex N = 740	Model 2 + education N = 740	Model 3 + age-11 IQ N = 698	Model 4 + current fluid ability N = 694	Model 5 + occup class N = 679	Model 6 + health status N = 677
General functional health literacy	0.774 (0.650 to 0.922)**	0.746 (0.615 to 0.905)**	0.738 (0.585 to 0.931)*	0.871 (0.674 to 1.125)	0.911 (0.700 to 1.186)	0.950 (0.725 to 1.245)
Age	0.897 (0.678 to 1.187)	0.893 (0.675 to 1.182)	0.902 (0.677 to 1.200)	0.885 (0.663 to 1.182)	0.933 (0.693 to 1.257)	0.942 (0.700 to 1.266)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.276 (0.886 to 1.838)	1.272 (0.883 to 1.833)	1.238 (0.852 to 1.799)	1.327 (0.912 to 1.930)	1.178 (0.778 to 1.784)	1.337 (0.869 to 2.056)
Years of education		1.080 (0.909 to 1.284)	1.119 (0.936 to 1.339)	1.134 (0.948 to 1.357)	1.240 (1.019 to 1.508)*	1.255 (1.030 to 1.528)*
Age-11 IQ			0.999 (0.984 to 1.014)	1.006 (0.991 to 1.022)	1.006 (0.991 to 1.022)	1.007 (0.992 to 1.023)
Fluid ability				0.687 (0.531 to 0.887)**	0.707 (0.543 to 0.921)*	0.770 (0.589 to 1.007)
Occupational class						
Professional					Reference	Reference
Managerial/technical					1.901 (0.962 to 3.756)	1.870 (0.945 to 3.700)
Skilled: non-manual					2.076 (0.979 to 4.401)	2.192 (1.035 to 4.640)*
Skilled: manual					3.134 (1.405 to 6.991)**	2.823 (1.252 to 6.365)*
Partly skilled/ unskilled manual					1.824 (0.580 to 5.741)	1.759 (0.557 to 5.561)
Self-rated health						
Very good/excellent						Reference
Good						1.152 (0.733 to 1.810)
Fair/poor						2.229 (1.229 to 4.042)**
HADS total score						0.975 (0.931 to 1.022)
Townsend disability						1.128 (1.040 to 1.225)**

* $p < .05$, ** $p < .01$.

General functional health literacy, general measure of functional health literacy created by entering the REALM, S-TOFHLA and NVS into a PCA; IQ, Intelligence Quotient; occup class, Occupational class; HADS, Hospital Anxiety and Depression Scale.

Supplementary Table 6 Hazard ratios (95% confidence intervals) for the association between REALM and mortality, controlling for sociodemographic, cognitive ability, and health status variables. Models are run on a sub-sample participants with all variables of interest (N = 728).

	Model 1 Age and sex	Model 2 + education	Model 3 + age-11 IQ	Model 4 + current fluid ability	Model 5 + occup class	Model 6 + health status
REALM	0.944 (0.894 to 0.997)*	0.946 (0.894 to 1.001)	0.959 (0.900 to 1.021)	0.966 (0.904 to 1.033)	0.969 (0.904 to 1.039)	0.996 (0.924 to 1.074)
Age	1.002 (0.763 to 1.316)	1.001 (0.762 to 1.315)	0.999 (0.761 to 1.312)	0.931 (0.704 to 1.231)	0.930 (0.700 to 1.234)	0.933 (0.704 to 1.235)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.303 (0.897 to 1.892)	1.304 (0.898 to 1.893)	1.289 (0.887 to 1.872)	1.358 (0.935 to 1.971)	1.224 (0.815 to 1.836)	1.364 (0.898 to 2.073)
Years of education		0.981 (0.831 to 1.158)	1.010 (0.848 to 1.204)	1.077 (0.902 to 1.287)	1.203 (0.994 to 1.455)	1.232 (1.018 to 1.492)*
Age-11 IQ			0.993 (0.980 to 1.006)	1.007 (0.992 to 1.023)	1.009 (0.993 to 1.025)	1.008 (0.993 to 1.024)
Fluid ability				0.632 (0.503 to 0.794)***	0.666 (0.528 to 0.841)**	0.727 (0.574 to 0.922)**
Occupational class						
Professional					Reference	Reference
Managerial/technical					2.201 (1.118 to 4.333)*	2.218 (1.127 to 4.365)*
Skilled: non-manual					2.482 (1.175 to 5.245)*	2.596 (1.232 to 5.474)*
Skilled: manual					3.570 (1.627 to 7.837)**	3.393 (1.532 to 7.516)**
Partly skilled/ unskilled manual					2.023 (0.641 to 6.388)	2.067 (0.656 to 6.510)
Self-rated health						
Very good/excellent						Reference
Good						1.153 (0.742 to 1.791)
Fair/poor						2.071 (1.147 to 3.739)*
HADS total score						0.972 (0.929 to 1.018)
Townsend disability						1.133 (1.044 to 1.229)**

**p* < .05, ***p* < .01, ****p* < .001.

REALM, Rapid Estimate of Adult Literacy in Medicine; IQ, Intelligence Quotient; occup class, Occupational class; HADS, Hospital Anxiety and Depression Scale.

Supplementary Table 7 Hazard ratios (95% confidence intervals) for the association between S-TOFHLA and mortality, controlling for sociodemographic, cognitive ability, and health variables. Models are run on a subsample of participants with all variables of interest (N = 680).

	Model 1 Age and sex	Model 2 + education	Model 3 + age-11 IQ	Model 4 + current fluid ability	Model 5 + occup class	Model 6 + health status
S-TOFHLA	0.947 (0.917 to 0.978)**	0.945 (0.914 to 0.977)**	0.949 (0.913 to 0.985)**	0.969 (0.930 to 1.010)	0.975 (0.934 to 1.018)	0.998 (0.953 to 1.046)
Age	0.924 (0.688 to 1.242)	0.925 (0.688 to 1.242)	0.927 (0.690 to 1.245)	0.911 (0.677 to 1.224)	0.919 (0.681 to 1.240)	0.936 (0.697 to 1.256)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.304 (0.893 to 1.902)	1.306 (0.895 to 1.905)	1.298 (0.889 to 1.896)	1.356 (0.928 to 1.981)	1.233 (0.814 to 1.866)	1.352 (0.881 to 2.074)
Years of education		1.033 (0.874 to 1.222)	1.046 (0.875 to 1.250)	1.092 (0.911 to 1.309)	1.208 (0.994 to 1.469)	1.249 (1.026 to 1.520)*
Age-11 IQ			0.997 (0.983 to 1.011)	1.006 (0.991 to 1.022)	1.007 (0.992 to 1.023)	1.006 (0.991 to 1.022)
Fluid ability				0.699 (0.545 to 0.895)**	0.717 (0.556 to 0.923)*	0.759 (0.587 to 0.982)*
Occupational class						
Professional					Reference	Reference
Managerial/technical					1.853 (0.935 to 3.670)	1.844 (0.931 to 3.650)
Skilled: non-manual					2.105 (0.992 to 4.464)	2.207 (1.042 to 4.673)*
Skilled: manual					3.038 (1.358 to 6.796)**	2.881 (1.275 to 6.509)*
Partly skilled/ unskilled manual					1.755 (0.556 to 5.541)	1.773 (0.562 to 5.598)
Self-rated health						
Very good/excellent						Reference
Good						1.147 (0.728 to 1.807)
Fair/poor						2.209 (1.216 to 4.014)**
HADS total score						0.974 (0.930 to 1.021)
Townsend disability						1.131 (1.039 to 1.232)**

*$p < .05$, **$p < .01$.

S-TOFHLA, Shortened Test of Functional Health Literacy in Adults; IQ, Intelligence Quotient; occup class, Occupational class; HADS, Hospital Anxiety and Depression Scale.

Supplementary Table 8 Hazard ratios (95% confidence intervals) for the association between NVS and mortality, controlling for sociodemographic, cognitive ability, and health variables. Models are run on a sub-sample of participants with all variables of interest (N = 724).

	Model 1 Age and sex	Model 2 + education	Model 3 + age-11 IQ	Model 4 + current fluid ability	Model 5 + occup class	Model 6 + health status
NVS	0.880 (0.800 to 0.968)**	0.875 (0.790 to 0.968)*	0.887 (0.796 to 0.989)*	0.953 (0.850 to 1.070)	0.960 (0.854 to 1.079)	0.961 (0.853 to 1.082)
Age	0.993 (0.756 to 1.306)	0.993 (0.756 to 1.306)	0.992 (0.754 to 1.304)	0.944 (0.714 to 1.248)	0.940 (0.709 to 1.248)	0.937 (0.708 to 1.242)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.346 (0.933 to 1.943)	1.346 (0.933 to 1.943)	1.326 (0.916 to 1.919)	1.373 (0.950 to 1.986)	1.228 (0.820 to 1.840)	1.355 (0.893 to 2.057)
Years of education		1.029 (0.866 to 1.222)	1.048 (0.876 to 1.253)	1.084 (0.905 to 1.298)	1.212 (0.999 to 1.470)	1.242 (1.023 to 1.508)*
Age-11 IQ			0.995 (0.982 to 1.008)	1.006 (0.992 to 1.021)	1.008 (0.993 to 1.023)	1.009 (0.994 to 1.023)
Fluid ability				0.645 (0.506 to 0.822)***	0.678 (0.529 to 0.869)**	0.748 (0.580 to 0.966)*
Occupational class						
Professional					Reference	Reference
Managerial/technical					2.211 (1.123 to 4.354)*	2.243 (1.140 to 4.414)*
Skilled: non-manual					2.435 (1.152 to 5.146)*	2.593 (1.231 to 5.463)*
Skilled: manual					3.590 (1.637 to 7.874)**	3.360 (1.522 to 7.415) **
Partly skilled/ unskilled manual					2.101 (0.668 to 6.604)	2.086 (0.661 to 6.578)
Self-rated health						
Very good/excellent						Reference
Good						1.175 (0.756 to 1.826)
Fair/poor						2.099 (1.167 to 3.775)*
HADS total score						0.973 (0.930 to 1.018)
Townsend disability						1.132 (1.044 to 1.228)**

**p* < .05, ***p* < .01.

NVS, Newest Vital Sign; IQ, Intelligence Quotient; occup class, Occupational class; HADS, Hospital Anxiety and Depression Scale.

Supplementary Table 9 Hazard ratios (95% confidence intervals) for the association between general functional health literacy and mortality, controlling for sociodemographic, cognitive ability, and health variables. Models are run on a sub-sample of participants with all variables of interest (N = 677).

	Model 1 Age and sex	Model 2 + education	Model 3 + age-11 IQ	Model 4 + current fluid ability	Model 5 + occup class	Model 6 + health status
General health literacy	0.769 (0.640 to 0.924)**	0.736 (0.602 to 0.901)**	0.742 (0.586 to 0.939)*	0.868 (0.669 to 1.126)	0.903 (0.694 to 1.176)	0.950 (0.725 to 1.245)
Age	0.940 (0.701 to 1.260)	0.937 (0.699 to 1.256)	0.937 (0.699 to 1.257)	0.925 (0.688 to 1.243)	0.934 (0.692 to 1.260)	0.942 (0.700 to 1.266)
Sex						
Female	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.264 (0.863 to 1.851)	1.256 (0.858 to 1.840)	1.255 (0.857 to 1.839)	1.328 (0.906 to 1.947)	1.205 (0.794 to 1.829)	1.337 (0.869 to 2.056)
Years of Education		1.096 (0.915 to 1.312)	1.098 (0.914 to 1.320)	1.114 (0.927 to 1.340)	1.229 (1.010 to 1.497)*	1.255 (1.030 to 1.528)*
Age-11 IQ			0.999 (0.984 to 1.014)	1.006 (0.991 to 1.022)	1.007 (0.991 to 1.023)	1.007 (0.992 to 1.023)
Fluid ability				0.692 (0.534 to 0.898)**	0.708 (0.543 to 0.922)*	0.770 (0.589 to 1.007)
Occupational class						
Professional					Reference	Reference
Managerial/technical					1.863 (0.941 to 3.689)	1.870 (0.945 to 3.700)
Skilled: non-manual					2.070 (0.976 to 4.390)	2.192 (1.035 to 4.640)*
Skilled: manual					3.072 (1.377 to 6.857)**	2.823 (1.252 to 6.365)*
Partly skilled/ unskilled manual					1.794 (0.570 to 5.649)	1.759 (0.557 to 5.561)
Self-rated health						
Very good/excellent						Reference
Good						1.152 (0.733 to 1.810)
Fair/poor						2.229 (1.229 to 4.042)**
HADS total score						0.975 (0.931 to 1.022)
Townsend disability						1.128 (1.040 to 1.225)**

$*p < .05$, $**p < .01$.

General health literacy, general measure of health literacy created by entering the REALM, S-TOFHLA and NVS into a PCA; IQ, Intelligence Quotient; occup class, Occupational class; HADS, Hospital Anxiety and Depression Scale.

Appendix 3. Supplementary material for Section 7.2

Twin Research and Human Genetics

Genetic contributions to health literacy

Chloe Fawns-Ritchie

Gail Davies

Saskia P Hagenaars

Ian J Deary

Sources of genetic results from genome-wide association studies

AlcGen/CHARGE+

Alcohol consumption data were obtained from the AlcGen/CHARGE+ consortium.

CHARGE-Aging and Longevity

Gait speed data were obtained from the CHARGE-Aging and Longevity consortium.

Longevity data have been provided by the CHARGE-Aging and Longevity consortium. Longevity was defined as reaching age 90 years or older. Genotyped participants who died between the ages of 55 and 80 years were used as the control group. There were 6,036 participants who achieved longevity and 3757 participants in the control group across participating studies in the discovery meta-analysis.

Broer L, Buchman AS, Deelen J, Evans DS, Faul JD, Lunetta KL, Sebastiani P, Smith JA, Smith AV, Tanaka T, Yu L, Arnold AM, Aspelund T, Benjamin EJ, De Jager PL, Eirkisdottir G, Evans DA, Garcia ME, Hofman A, Kaplan RC, Kardia SL, Kiel DP, Oostra BA, Orwoll ES, Parimi N, Psaty BM, Rivadeneira F, Rotter JI, Seshadri S, Singleton A, Tiemeier H, Uitterlinden AG, Zhao W, Bandinelli S, Bennett DA, Ferrucci L, Gudnason V, Harris TB, Karasik D, Launer LJ, Perls TT, Slagboom PE, Tranah GJ, Weir DR, Newman AB, van Duijn CM and Murabito JM. GWAS of Longevity in CHARGE Consortium Confirms APOE and FOXO3 Candidacy. *Journals of Gerontology. Series A Biolological Sciences and Medical Sciences*. 2015;70:110-8.

Acknowledgments: The CHARGE Aging and Longevity working group analysis of the longevity phenotype was funded through the individual contributing studies. The working group thanks all study participants and study staff.

CHARGE-Cognitive working group/COGENT

For general cognitive function a meta-analysis excluding ELSA was conducted by the CHARGE and COGENT consortia and the summary data were made available for the present study.

CHIC

Childhood cognitive ability data were obtained from the CHIC consortium.

DIAGRAM

Type 2 diabetes data were obtained from the DIAGRAM consortium.

GIANT

BMI and waist-to-hip ratio data were obtained from the GIANT consortium.

International Genomics of Alzheimer's Project (IGAP)

Alzheimer's disease data were obtained from (IGAP)

Material and methods: International Genomics of Alzheimer's Project (IGAP) is a large two-stage study based upon genome-wide association studies (GWAS) on individuals of European ancestry. In stage 1, IGAP used genotyped and imputed data on 7 055 881 single nucleotide polymorphisms (SNPs) to meta-analyse four previously-published GWAS datasets consisting of 17,008 Alzheimer's disease cases and 37,154 controls (The European Alzheimer's disease Initiative – EADI the Alzheimer Disease Genetics Consortium – ADGC The Cohorts for Heart and Aging Research in Genomic Epidemiology consortium – CHARGE The Genetic and Environmental Risk in AD consortium – GERAD). In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. Finally, a meta-analysis was performed combining results from stages 1 & 2.

Acknowledgments: We thank the International Genomics of Alzheimer's Project (IGAP) for providing summary results data for these analyses. The investigators within IGAP contributed to the design and implementation of IGAP and/or provided data but did not participate in analysis or writing of this report. IGAP was made possible by the generous participation of the control subjects, the patients, and their families. The i–Select chips was funded by the French National Foundation on Alzheimer's disease and related disorders. EADI was supported by the LABEX (laboratory of excellence program investment for the future) DISTALZ grant, Inserm, Institut Pasteur de Lille, Université de Lille 2 and the Lille University Hospital. GERAD was supported by the Medical Research Council (Grant n° 503480), Alzheimer's Research UK (Grant n° 503176), the Wellcome Trust (Grant n° 082604/2/07/Z) and German Federal Ministry of Education and Research (BMBF): Competence Network Dementia (CND) grant n° 01GI0102, 01GI0711, 01GI0420. CHARGE was partly supported by the NIH/NIA grant R01 AG033193 and the NIA AG081220 and AGES contract N01–AG–12100, the NHLBI grant R01 HL105756, the Icelandic Heart Association, and the Erasmus Medical Center and Erasmus University. ADGC was supported by the NIH/NIA grants: U01 AG032984, U24 AG021886, U01 AG016976, and the Alzheimer's Association grant ADGC–10–196728.

Psychiatric Genetics Consortium

Schizophrenia and major depressive disorder data were obtained from the Psychiatric Genetics Consortium.

Social Science Genetic Association Consortium

Years of schooling data were obtained from the Social Science Genetic Association Consortium.

SpiroMeta/CHARGE-Pulmonary

Lung function (Forced expiratory volume in 1 second) data were obtained from the SpiroMeta and CHARGE-Pulmonary consortia.

The Genetics of Personality Consortium

Conscientiousness data were obtained from the Genetics of Personality consortium.

The Neale Lab

High blood pressure data were obtained from the Neale Lab.

Tobacco and Genetics Consortium

Smoking status (ever smoked) data were obtained from the Tobacco and Genetics Consortium.

Supplementary Table S1. Sources of genetic results from genome-wide association studies

Phenotype	Source	URL	Reference	GWAS n
General cognitive ability	CHARGE/COGENT		Davies et al. (2018). *Nature Communications*, *9*, 2098. https://doi.org/10.1038/s41467-018-04362-x	300,486
Verbal-numerical reasoning	UK Biobank	https://www.ccace.ed.ac.uk/node/335	Davies et al. (2018). *Nature Communications*, *9*, 2098. https://doi.org/10.1038/s41467-018-04362-x	168,033
Reaction time	UK Biobank	https://www.ccace.ed.ac.uk/node/335	Davies et al. (2018). *Nature Communications*, *9*, 2098. https://doi.org/10.1038/s41467-018-04362-x	330,069
Childhood IQ	CHIC	https://www.thessgac.org/data	Benyamin et al. (2014). *Molecular Psychiatry*, *19*, 253-258. https://doi.org/10.1038/mp.2012.184	17,989
Years of schooling	Social Science Genetic Association Consortium	https://www.thessgac.org/data	Okbay et al. (2016). *Nature*, *533*, 593. https://doi.org/10.1038/nature17671	293,723
Social deprivation	UK Biobank	https://www.ccace.ed.ac.uk/node/335	Hill et al. (2016). *Current Biology*, *26*, 3083-3089. http://dx.doi.org/10.1016/j.cub.2016.09.035	112,151
Self-rated health	UK Biobank	https://www.ccace.ed.ac.uk/node/335	Harris et al. (2017). *International Journal of Epidemiology*, *46*, 994-1009. https://doi.org/10.1093/ije/dyw219	111,749

Forced expiratory volume in 1 second (FEV_1)	SpiroMeta/CHARGE-Pulmonary	https://grasp.nhlbi.nih.gov/FullResults.aspx	Soler Artigas et al. (2011). *Nature Genetics*, *43*, 1082. https://doi.org/10.1038/ng.941	48,201
Longevity	CHARGE-Aging and Longevity working group	https://grasp.nhlbi.nih.gov/FullResults.aspx	Broer et al. (2015). *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, *70*, 110-118. https://doi.org/10.1093/gerona/glu166	6,036 cases 3,757 controls
Gait speed	CHARGE-Aging and Longevity working group	https://grasp.nhlbi.nih.gov/FullResults.aspx	Ben-Avraham et al. (2017). *Aging*, *9*, 209. https://doi.org/10.18632/aging.101151	31,478
BMI	GIANT	https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	Locke et al. (2015). *Nature*, *518*, 197-206. https://doi.org/10.1038/nature14177	339,224
Waist-to-hip ratio	GIANT	http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files	Shungin et al. (2015). *Nature*, *518*, 187-196. https://doi.org/10.1038/nature14132	224,459
Type 2 diabetes	DIAGRAM	http://www.diagram-consortium.org/downloads.html	Scott et al. (2017). *Diabetes*, *66*, 2888-2902. https://doi.org/10.2337/db16-1253	26,676 cases 132,532 controls
High blood pressure	Neale Lab	https://docs.google.com/spreadsheets/d/1b3oGI2lUt57BcuHttWaZotQcI0-mBRPyZihz87Ms_No/edit#gid=1209628142	http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samples-in-the-uk-biobank	336,683
Smoking status	Tobacco and Genetics Consortium	https://www.med.unc.edu/pgc/results-and-downloads	Furberg et al. (2010). *Nature Genetics*, 42, 441-447. https://doi.org/10.1038/ng.571	74,053
Alcohol consumption	AlcGen/CHARGE +	https://grasp.nhlbi.nih.gov/FullResults.aspx	Schumann et al. (2016). *PNAS*, *113*, 14372-14377.	70,460

			https://doi.org/10.1073/pnas.1611243113	
Alzheimer's disease	International Genomics of Alzheimer's Project (IGAP)	http://web.pasteur-lille.fr/en/recherche/u744/igap/igap_download.php	Lambert et al. (2013). *Nature Genetics*, *45*, 1452-1458. https://doi.org/10.1038/ng.2802	17,008 cases 37,154 controls
Major depressive disorder	Psychiatric Genetics Consortium (PGC)	https://www.med.unc.edu/pgc/results-and-downloads/downloads	Wray et al. (2018). *Nature Genetics* 2018, *50*, 668-681. https://doi.org/10.1038/s41588-018-0090-3	135,458 cases 344,901 controls
Schizophrenia	Psychiatric Genetics Consortium (PGC)	https://www.med.unc.edu/pgc/results-and-downloads/downloads	Ripke et al. (2014). *Nature*, *511*, 421-427. https://doi.org/10.1038/nature13595	36,989 cases 113,075 controls
Neuroticism	UK Biobank	https://www.ccace.ed.ac.uk/node/335	Luciano et al. (2018). *Nature Genetics*, *50*, 6-11. https://doi.org/10.1038/s41588-017-0013-8	329,821
Conscientiousness	Genetics of Personality Consortium (GPC)	http://eagle-i.itmat.upenn.edu/sweet/provider?uri=http://eagle-i.itmat.upenn.edu/i/00000155-e19e-5a51-c956-e86e80000000	de Moor et al. (2017). *Molecular Psychiatry*, *17*, 337-349. https://doi.org/10.1038/mp.2010.128	17,375

Note. ELSA participants were removed and the GWAS of general cognitive ability was re-run for the purpose of this analysis (n = 286,054).

Supplementary methods

To investigate whether health literacy polygenic profile scores predict health literacy in an independent sample, we used data from 1,005 genotyped participants in the Lothian Birth Cohort 1936 (LBC1936) study. Polygenic profile scores were created using the health literacy GWAS results and we used these polygenic scores to predict scores on a health literacy test, general cognitive ability and years of schooling in LBC1936 participants.

Health literacy. The Newest Vital Sign (NVS; Weiss et al., 2005) was administered to 790 LBC1936 participants at wave 2 (mean age = 70.9, SD = 0.7). In this brief health literacy test, participants are presented with a label for a container of ice cream. The participants are then asked 6 questions about the information provided on this label. The NVS is similar in content and length to the health literacy measure used in ELSA as it is a brief test health-related reading comprehension and numeracy. The score is the number of correctly answered questions (maximum score = 6). A total of 690 participants had genotyping data and scores on the Newest Vital Sign and were used as the analytic sample in the analysis examining the association between health literacy polygenic score and Newest Vital Sign.

Cognitive ability. The following cognitive tests, administered at wave 1 when participants were a mean age of 69.5 (SD = 0.8), were used here: Moray House Test Number 12 (Scottish Council for Research in Education, 1949), the Wechsler Memory Scale-III (WMS-III) Logical Memory test (Wechsler, 1998), WMS-III Spatial Span test (Wechsler, 1998), four-choice reaction time (Deary, Der, & Ford, 2001), and verbal fluency. The Moray House Test (Scottish Council for Research in Education, 1949) is a 45-minute test of general intelligence that includes items assessing verbal reasoning and spatial ability. Total scores were corrected for age in days at testing and converted to IQ-type scores (mean = 100, SD = 15). In the Logical Memory test (Wechsler, 1998), participants were read a paragraph containing 25 elements. The participants had to recall the story immediately and after a delay. The score used here is the total elements remembered across both immediate and delayed recall. The

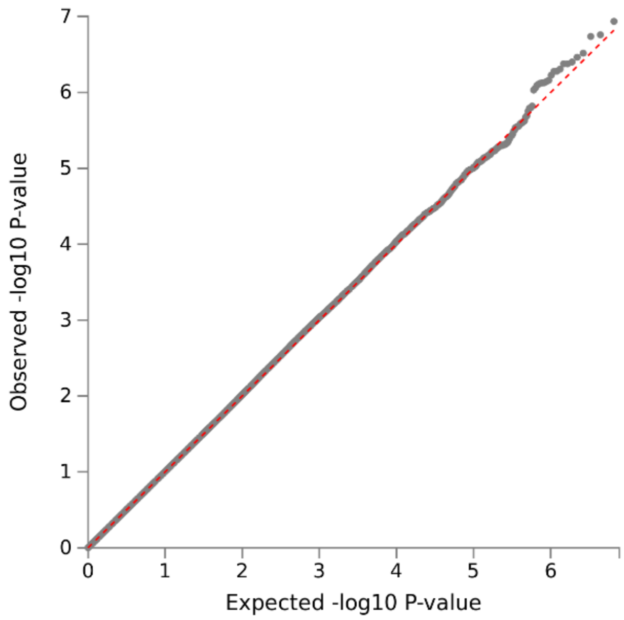
Spatial Span test (Wechsler, 1998) measures non-verbal working memory. The tester touches the top of a number of blocks in a specific sequence. The participant is then to tap the blocks in the same order, or in the reverse order. The sequences become progressively longer, until the participant is no longer able to remember the sequence. The score is the number of trials in which the participant correctly taps the sequence in the same or reversed order. In the four-choice reaction time test (Deary et al., 2001), participants were presented with a box with a screen display on it and keys underneath. A number (1, 2, 3, or 4) appears on the screen and the participant has to push the key that corresponds to the number as quickly as possible. The score is the mean time (in milliseconds) to press the correct key. In the verbal fluency test, participants are asked to name as many words as they can beginning with the letters C, F and L. Participant are given one minute per letter and the score is the total number or words named within the time limit across the three trials.

Scores on these cognitive tests were entered into a principal component analysis. The first unrotated principal component accounted for 45.4% of the total variance and scores on this first unrotated principal component were saved and used as a measure of cognitive ability. Test loadings were: Moray House Test = 0.83; Logical memory = 0.65; Spatial Span = 0.63; Four-choice reaction time = -0.66; Verbal fluency = 0.57. A total of 934 LBC1936 participants had genotyping data and cognitive ability scores and were used as the analytic sample in the analysis examining the association between health literacy polygenic score and cognitive ability.

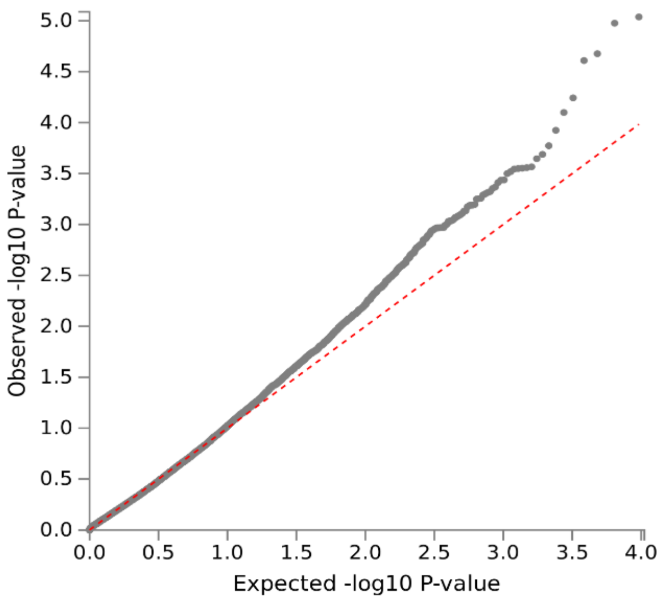
Educational attainment. At wave 1, LBC1936 participants were asked the number of years of full-time education they had completed. A total of 934 LBC1936 participants had genotyping and educational attainment data and were used as the analytic sample in the analysis examining the association between health literacy polygenic score and educational attainment.

Supplementary Figure S1. Quantile-quantile plots for a) health literacy GWAS, and b) health literacy gene-based analysis

a



b



Supplementary Table S2. Association between polygenic profile score for health literacy with the Newest Vital Sign, cognitive ability, and years of schooling, controlling for age*, sex, and 4 genetic principal components

Trait	Threshold	β	R2	p-value	Number of SNPs
Newest Vital Sign	0.01	-0.013	-0.0013	0.735	3042
	0.05	-0.048	0.0009	0.203	13091
	0.1	-0.047	0.0008	0.217	24430
	0.5	-0.020	-0.0011	0.606	96920
	1	-0.015	-0.0012	0.693	152148
Cognitive ability	0.01	0.039	0.0005	0.219	3042
	0.05	-0.004	-0.0010	0.897	13091
	0.1	-0.007	-0.0001	0.832	24430
	0.5	0.022	-0.0005	0.496	96920
	1	0.019	-0.0007	0.556	152148
Years of schooling	0.01	0.060	0.0025	0.066	3042
	0.05	0.008	-0.0010	0.818	13091
	0.1	0.018	-0.0008	0.593	24430
	0.5	0.010	-0.0010	0.766	96920
	1	0.005	-0.0010	0.873	152148

Note: R2 is calculated by subtracting the value of a model containing only the covariates (age, sex, and 4 genetic principal components) from the model including the polygenic profile score and covariates.

*Age in days at wave 1 was used in the model with cognitive ability and years of schooling. Age in days at wave 2 was used in the model with Newest Vital Sign.

Supplementary Table S3. Association between polygenic profile score for cognitive, socioeconomic, health and personality traits with having adequate health literacy, controlling for age, sex and 15 genetic principal components

				95% CI				
Trait category	Trait	Threshold	OR	Lower	Upper	R2*	p-value†	Number of SNPs
Cognitive traits and proxies	General cognitive ability	0.01	1.283	1.206	1.365	0.0150	**2.93×10^{-14}**	10644
		0.05	1.302	1.225	1.384	0.0173	**3.67×10^{-15}**	26498
		0.1	1.332	1.254	1.416	0.0208	**2.93×10^{-14}**	40550
		0.5	1.339	1.261	1.422	0.0219	**3.67×10^{-15}**	113154
		1	1.339	1.261	1.422	0.0219	**3.67×10^{-15}**	163060
	Verbal-numerical reasoning	0.01	1.234	1.157	1.316	0.0099	**1.03×10^{-9}**	9366
		0.05	1.298	1.219	1.382	0.0161	**4.92×10^{-15}**	24800
		0.1	1.281	1.204	1.362	0.0149	**3.30×10^{-14}**	38737
		0.5	1.304	1.228	1.385	0.0179	**3.67×10^{-15}**	11860
		1	1.302	1.226	1.383	0.0177	**3.67×10^{-15}**	163279
	Reaction time	0.01	0.999	0.944	1.057	0.0000	0.9980	7519
		0.05	0.982	0.928	1.039	0.0001	0.6334	21928
		0.1	0.976	0.923	1.034	0.0002	0.5487	35522
		0.5	0.954	0.902	1.010	0.0006	0.2504	109803
		1	0.957	0.904	1.013	0.0005	0.3048	163258

	Childhood IQ	0.01	1.044	0.986	1.106	0.0005	0.3080	2476
		0.05	1.025	0.968	1.085	0.0002	0.5487	10086
		0.1	1.038	0.980	1.099	0.0004	0.3945	18219
		0.5	1.057	0.998	1.120	0.0009	0.1548	68420
		1	1.061	1.001	1.123	0.0010	0.1281	105819
	Years of schooling	0.01	1.242	1.172	1.316	0.0129	**1.73×10^{-12}**	8258
		0.05	1.262	1.191	1.337	0.0148	**4.16×10^{-14}**	22772
		0.1	1.285	1.212	1.362	0.0171	**3.67×10^{-15}**	36365
		0.5	1.270	1.198	1.346	0.0155	**1.36×10^{-14}**	109535
		1	1.265	1.194	1.341	0.0151	**2.93×10^{-14}**	161726
Socioeconomic measures	Social deprivation	0.01	0.970	0.916	1.028	0.0003	0.4530	3910
		0.05	0.980	0.926	1.038	0.0001	0.6143	15885
		0.1	1.003	0.947	1.062	0.0000	0.9720	28748
		0.5	1.000	0.945	1.059	0.0000	0.9980	106152
		1	1.000	0.945	1.059	0.0000	0.9980	163239
General health status	Self-rated health	0.01	0.947	0.895	1.003	0.0008	0.1626	5052
		0.05	0.932	0.880	0.986	0.0014	0.0760	17812
		0.1	0.923	0.871	0.977	0.0018	**0.0359**	31018

	0.5	0.940	0.888	0.996	0.0011	0.1200	107379
	1	0.938	0.886	0.993	0.0011	0.1104	163268
FEV1	0.01	0.979	0.919	1.042	0.0001	0.6143	3185
	0.05	0.979	0.923	1.039	0.0001	0.6143	13275
	0.1	0.941	0.887	0.998	0.0010	0.1281	24885
	0.5	0.938	0.885	0.995	0.0011	0.1200	101307
	1	0.932	0.879	0.988	0.0013	0.0880	160612
Longevity	0.01	0.976	0.921	1.034	0.0002	0.5487	3349
	0.05	0.970	0.915	1.029	0.0002	0.4530	14278
	0.1	0.974	0.918	1.033	0.0002	0.5211	26363
	0.5	0.990	0.932	1.051	0.0000	0.8353	102168
	1	0.990	0.932	1.051	0.0000	0.8353	158944
Gait	0.01	1.002	0.945	1.063	0.0000	0.9848	3451
	0.05	0.991	0.935	1.051	0.0000	0.8630	14469
	0.1	0.998	0.941	1.058	0.0000	0.9858	26664
	0.5	1.000	0.943	1.060	0.0000	0.9980	101168
	1	1.003	0.946	1.064	0.0000	0.9720	156574
BMI	0.01	0.975	0.921	1.032	0.0002	0.5211	4194

		0.05	0.971	0.917	1.028	0.0002	0.4530	13316
		0.1	0.965	0.911	1.022	0.0004	0.4070	23826
		0.5	0.942	0.889	0.998	0.0010	0.1281	97257
		1	0.948	0.894	1.004	0.0008	0.1674	157730
	Waist-to-hip ratio	0.01	0.997	0.941	1.057	0.0000	0.9720	3714
		0.05	0.985	0.929	1.044	0.0001	0.7144	13918
		0.1	0.968	0.914	1.026	0.0003	0.4481	26321
		0.5	0.968	0.913	1.025	0.0003	0.4417	100048
		1	0.971	0.916	1.029	0.0002	0.4530	156877
Chronic diseases	Type 2 diabetes	0.01	1.029	0.971	1.090	0.0002	0.4729	5265
		0.05	1.043	0.984	1.105	0.0005	0.3217	17675
		0.1	1.036	0.977	1.097	0.0003	0.4263	31755
		0.5	1.032	0.973	1.094	0.0003	0.4530	108370
		1	1.031	0.973	1.093	0.0003	0.4530	163097
	High blood pressure	0.01	1.022	0.965	1.083	0.0001	0.5979	9881
		0.05	1.038	0.980	1.099	0.0004	0.3945	25216
		0.1	1.056	0.997	1.118	0.0008	0.1648	38804
		0.5	1.033	0.976	1.095	0.0003	0.4417	111002

		1	1.035	0.977	1.096	0.0003	0.4263	162052
Health behaviours	Smoking status	0.01	0.994	0.940	1.053	0.0000	0.9496	4065
		0.05	0.997	0.942	1.055	0.0000	0.9720	16056
		0.1	0.961	0.908	1.017	0.0004	0.3463	28662
		0.5	0.941	0.888	0.996	0.0011	0.1200	102996
		1	0.944	0.891	0.999	0.0010	0.1281	155523
	Alcohol consumption	0.01	0.996	0.938	1.058	0.0000	0.9720	3806
		0.05	0.979	0.919	1.042	0.0001	0.6148	15198
		0.1	0.955	0.895	1.017	0.0005	0.3217	27446
		0.5	0.940	0.880	1.004	0.0008	0.1648	101931
		1	0.944	0.884	1.008	0.0007	0.2071	156151
Neuro-psychiatric disorders	Alzheimer's disease	0.01	1.036	0.979	1.097	0.0004	0.4046	4232
		0.05	1.034	0.977	1.095	0.0003	0.4263	16247
		0.1	1.044	0.986	1.105	0.0005	0.3080	29079
		0.5	1.022	0.965	1.082	0.0001	0.5978	104309
		1	1.016	0.960	1.076	0.0001	0.6947	157411
	Alzheimer's disease (500 kb)	0.01	1.034	0.977	1.094	0.0003	0.4263	4189
		0.05	1.032	0.975	1.093	0.0003	0.4466	16192

		0.1	1.043	0.985	1.104	0.0005	0.3217	29019
		0.5	1.020	0.964	1.080	0.0001	0.6143	104237
		1	1.015	0.958	1.075	0.0001	0.7209	157330
	Major depressive disorder	0.01	1.000	0.938	1.056	0.0000	0.9711	5318
		0.05	0.936	0.884	0.992	0.0012	0.1104	18589
		0.1	0.940	0.887	0.996	0.0010	0.1210	31770
		0.5	0.942	0.889	0.998	0.0010	0.1281	108428
		1	0.937	0.885	0.993	0.0012	0.1104	162989
	Schizophrenia	0.01	0.939	0.882	1.000	0.0009	0.1356	9898
		0.05	0.920	0.866	0.977	0.0018	**0.0382**	25557
		0.1	0.922	0.868	0.979	0.0017	**0.0421**	39658
		0.5	0.907	0.854	0.962	0.0025	**0.0076**	112505
		1	0.905	0.853	0.960	0.0026	**0.0062**	162771
Personality traits	Neuroticism	0.01	0.939	0.885	0.996	0.0010	0.1210	9325
		0.05	0.934	0.881	0.991	0.0012	0.1030	24850
		0.1	0.927	0.875	0.983	0.0015	0.0602	38747
		0.5	0.933	0.881	0.989	0.0013	0.0921	111512
		1	0.939	0.886	0.995	0.0011	0.1200	163103

Conscientiousness	0.01	1.031	0.974	1.091	0.0003	0.4530	3097
	0.05	1.038	0.980	1.099	0.0004	0.3945	13315
	0.1	1.038	0.980	1.099	0.0004	0.3945	24885
	0.5	1.032	0.974	1.093	0.0003	0.4530	95148
	1	1.027	0.969	1.088	0.0002	0.5211	145404

Note: FEV1, forced expiratory volume in 1 second; BMI, body mass index.

*Nagelkerke Pseudo R2. R2 is calculated by subtracting the value of a model containing only the covariates (age, sex, and 15 genetic principal components) from the model including the polygenic profile score and covariates.

†p-values reported have been FDR-adjusted. FDR-adjusted significant p-values are shown in bold.

Supplementary References

Deary, I. J., Der, G., & Ford, G. (2001). Reaction times and intelligence differences: A population-based cohort study. *Intelligence, 29*(5), 389-399.

Scottish Council for Research in Education. (1949). *The trend of Scottish intelligence: A comparison of the 1947 and 1932 surveys of the intelligence of eleven-year-old pupils*. London, UK: University of London Press.

Wechsler, D. (1998). *WMS-III UK administration and scoring manual*. London, UK: Psychological Corporation.

Weiss, B. D., Mays, M. Z., Martz, W., Castro, K. M., DeWalt, D. A., Pignone, M. P., . . . Hale, F. A. (2005). Quick assessment of literacy in primary care: the newest vital sign. *The Annals of Family Medicine, 3*(6), 514-522. doi: 10.1370/afm.405