THE UNIVERSITY *of* EDINBURGH

Exploring Longitudinal Pathways from Intelligence to Morbidity and Mortality Risk

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Declaration

This thesis has been written and produced by me. The work presented within it is my own and has not been submitted for any other degree or professional qualification. Versions of some chapters have been published in a book or scientific journals, on which I am first author. Chapter 1 bears resemblance to the book chapter entitled "Cognitive Epidemiology Concepts, Evidence, and Future Directions" in *The Wiley-Blackwell Handbook of Individual Differences* (Calvin, Batty, & Deary, 2011). The systematic review and meta-analysis in Chapter 2 was published in the June 2011 issue of *International Journal of Epidemiology* (Calvin, Deary, et al., 2011). In June 2012 the studies in Chapters 3 and 4 were published online as a single article in the journal *Behavior Genetics* (Calvin, Deary, et al., 2012). The study in Chapter 5 using cohort data from the National Child Development Study 1958 was published in the November 2011 issue of *Health Psychology* (Calvin, Batty, Lowe, & Deary, 2011). The three journal articles are included at the end of the printed thesis, with licensed permissions to do so from the publishers. My main supervisors Ian Deary and David Batty approved submission of these studies for peer-review publication ahead of completing this thesis.

Catherine Calvin

Abstract

Human population-based studies of longitudinal design observe that higher intelligence in youth confers protection from premature mortality in adulthood. This field of study ("cognitive epidemiology"; Deary & Batty, 2007) has firmly established associations between intelligence and health outcomes, and has begun to address the likely mechanisms involved. The present thesis assessed some social, educational, and lifestyle factors that potentially confound and/or mediate the intelligence-mortality link.

First, I carried out a systematic review of longitudinal cohort studies reporting intelligence differences in youth in relation to adult mortality risk, and in meta-analysis I aggregated the effect sizes from 16. A one *SD* advantage in intelligence scores was associated with 24% (95% CI 23% to 25%) lower risk of death, during 17- to 69-year follow-up; this magnitude showed no sex differential. Socioeconomic status in early life did not explain the effect. Rather, the person's own occupational status in adulthood and educational attainment explained a third and a half of the association, respectively.

One issue in controlling for education, in such models, is its strong correlation with intelligence test performance, which could lead to statistical overadjustment. A second aspect of this thesis, therefore, addressed the nature of the intelligence-education covariance in two behaviour-genetic studies of large general population-based samples of schoolchildren from England and The Netherlands. Previous studies that reported intelligence—education genetic covariances were potentially biased in their use of twin self-selection or pre-selection sampling. Moreover, the analysis in this thesis used a novel statistical approach, and included non-twin data to represent fully the variance in performance scores of a population. Analysis of the English cohort confirmed the top end of estimates from previous studies: 76% to 88% of the phenotypic correlation was due to heritability. The Dutch cohort showed greater variance for equivalent estimates (33% to 100%). The results indicate a limit to the extent to which education and intelligence might be causative of one another suggesting caution in interpreting some of the substantive attenuation effects by education reported in the literature.

Third, I investigated pathways from intelligence to cardiovascular disease risk factors, given the consistent and robust finding that an advantage in intelligence relates to lower cardiovascular disease-outcomes. I used data from the 1958 National Child Development Study to investigate age-11 intelligence in association with inflammatory and haemostatic biomarker status at age 46 years. The results replicated inverse associations previously reported in an older age sample, and a one *SD* advantage in intelligence related to a 1.1mg/L decrease in C-reactive protein. The effect was largely mediated by lifestyle factors, including smoking, occupational status and abdominal obesity. In two further studies I used the west of Scotland Twenty-07 cohort, to investigate processing speeds among 16, 36 and 56 year-olds in relation to: (1) Inflammation, and (2) metabolic-risk, after 20 years. The advantage of experimental rather than psychometric measures of cognitive ability is their reduced cultural and social bias. Faster reaction time predicted lower systemic inflammation in the youngest male cohort, which appeared to be partially confounded by baseline smoking and socioeconomic status. Furthermore, advantage in reaction time performance in the young and middle-aged cohorts significantly predicted reduced metabolic risk. This was partially explained by occupational status, but retained statistical significance in some fully-adjusted models. A one *SD* advantage in age 16 simple reaction time variability, related to the 21% (95% CI 12% to 30%) reduced odds of metabolic syndrome by age 36 in the basic model, and this effect remained unchanged after controlling for all covariates.

The growing evidence for specific social and behavioural factors that mediate intelligence-to-mortality pathways are discussed, in respect of indirect evidence that underlying system integrity or early life confounding may contribute incrementally to the effect.

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Additional data were provided by Finn Rasmussen of the Karolinska Institute in Stockholm, Sweden who granted permission to use data from the Swedish Conscripts Study on mental ability scores and mortality for the purpose of producing the time-to-survival chart in Chapter 1. I also thank the following individuals for providing additional data for inclusion in the meta-analysis study of intelligence and mortality (Chapter 2): Tomas Hemmingsson, Tracey Holsinger, Diana Kuh, Anton Lager, Laurie Martin, Merete Osler, Brian O'Toole and Denny Vågerö.

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I dedicate this thesis to my parents for their love and encouragement.

Table of Contents

Publications

Calvin, C.M., Deary, I.J., Fenton, C., Roberts, B., 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., Lowe, G.D., Deary, I.J. (2011). Childhood intelligence and midlife inflammatory and hemostatic biomarkers: the National Child Development Study (1958) Cohort. *Health Psychology*, 30(6), 710-718.

Calvin, C.M., Deary, I.J., Webbink, D., Smith, P., Fernandes, C., Lee, S.H., Luciano, M., Visscher, P.M. (2012). Multivariate genetic analyses of cognition and academic achievement from two population samples of 174,000 and 166,000 school children. *Behavior Genetics*. doi 10.1007/s10519-012-9549-7.

List of Tables

List of Figures

Chapter 1
Introduction

Cognitive epidemiology defined

Cognitive epidemiology is a new field for the study of individual differences, attempting to understand associations between premorbid cognitive ability (I shall also use the terms intelligence, mental ability, IQ) and health outcomes, particularly morbidity and mortality. The concept of intelligence in association with health may be a familiar one. Evidence in the field of cognitive ageing has related somatic diseases to a subsequent decline in intellectual function (Arvanitakis, Wilson, & Bennett, 2006; Comijs et al., 2009; Kivipelto et al., 2005; Okereke et al., 2008; Rafnsson, Deary, Smith, Whiteman, & Fowkes, 2007; Yaffe et al., 2004). Cross-sectional studies pervade the health psychology literature demonstrating that mental performance and physical health variables significantly correlate. Examining the influences of individual differences in cognitive ability upon health is a more recent endeavour, with rapid progress in the last decade. Cognitive epidemiology began with the observation that scores on mental ability tests inversely correlated with the risk of all-cause mortality over a long-term follow-up. This finding has resonance for several disciplines. For differential psychologists it is further evidence for the predictive validity of general intelligence (*g*), the highly stable (Deary, Whalley, Lemmon, Crawford, & Starr, 2000) and heritable (Deary, Johnson, & Houlihan, 2009) trait that significantly correlates with other lifetime outcomes including educational attainment and career success (Deary, Strand, Smith, & Fernandes, 2007; Gottfredson, 1997; Schmidt & Hunter, 2004). For epidemiologists, clinicians and policy makers the observation has importance in its contribution to understanding health inequalities in populations. The field has gained momentum and already a large body of empirical work exists which is helping to map out the underlying mechanisms relating cognitive ability to health outcomes.

This chapter presents the latest empirical evidence from the field, and key issues that merit further investigation and understanding. Before doing so, two

important areas are covered. First, a brief historical context is presented on the events leading up to cognitive epidemiology becoming a defined area of research. Second, in recognition that the field brings together two main disciplines – differential psychology and epidemiology – I briefly introduce the psychology reader to some key concepts and methods in epidemiology. Evidence from the field's empirical work comes in the following order of presentation: Premorbid intelligence in relation to all-cause mortality; cause-specific mortality and morbidities; and, disease risk factors. The final section of this chapter discusses the likely mechanisms that may explain these associations, with attention given to methods that should help to consolidate these in the future.

A brief history

A paper by Maller (1933) is cited as the first observational study to report an inverse association between childhood mental ability scores and risk of mortality (Deary & Batty, 2006; Gottfredson, 2004). This took the average mental ability test scores of schools distributed among 310 geographical areas of New York City, linking them to mortality rates in 1930 for each region. The correlation was r = -.43, such that higher IQ scores were associated with lower mortality risk. The study was important in observing a trend, but it was 55 years later that one of the first known peer-reviewed empirical studies to use individual data on premorbid intelligence and adult mortality was published. The Australian Veterans Health Studies linked mental ability test scores of over 2,300 servicemen born between 1947 and 1953, with mortality records spanning 17 years after IQ testing (O'Toole, Adena, & Jones, 1988). The results showed that deceased ex-servicemen by follow-up had significantly lower mean scores on the Army Classification Test compared to those who were still alive at follow-up. The next published evidence followed 13 years later in the *British Medical Journal*, also reporting an inverse association between IQ and risk of mortality (Whalley & Deary, 2001). This study's cohort represented 80% of children (n = 2,230) born in Aberdeen, Scotland in 1921, who were part of the Scottish Mental Survey 1932 (SMS32). It was a population-wide study, which

applied the same intelligence test to almost every child in Scotland born in 1921. The follow-up period for mortality was 65 years. The authors reported a significant hazard ratio of 0.79 (95% CI 0.75 to 0.84) for the risk of mortality by 76 years of age, given one *SD* advantage in IQ scores at age 11, and a hazard ratio of 0.63 (95% CI 0.56 to 0.71) for all-cause mortality given a two *SD* advantage in IQ. This study heralded several recent studies in the field, and had some strengths: A population-representative cohort with long-term follow-up; publication in a general medical journal, which brought the IQ-mortality association to a wider readership; reporting hazard ratios for the risk of mortality – statistics more familiar to epidemiologists (see later section on *Measuring risk* for an explanation of hazard ratios, and related measures of risk) – which brought an individual differences measure into the arena of public health.

The contribution that individual differences in general cognitive ability could make to understanding health inequalities had been suggested before, although it was recognized that epidemiologists might not readily embrace this idea:

> [IQ]'s potential for informing public policy is grossly underappreciated. In part, this neglect is because intellectual assessment is typically focused on individuals (a hallmark of the psychometric approach) as distinct from populations (more of an epidemiological approach)" (Lubinski & Humphreys, 1997, p.159-160).

Opinion pieces followed, emphasizing the importance of cognitive ability to health outcomes (Gottfredson & Deary, 2004), and proposing possible mechanisms to explain the association (Batty & Deary, 2004). A theoretical review posited that intelligence might be the underlying cause of the well-documented socioeconomic inequalities in health (Gottfredson, 2004). The empirical work has continued, with existing large cohorts replicating the inverse intelligence-mortality link, giving further credibility to the basic finding. These have included (in publication date order): A second cohort of the SMS32 involving 922 men and women followed up for 69 years (Hart et al., 2003); the Danish Metropolit Study of 7,308 members, in which members completed IQ tests at 12 years and were followed up 33 years later (Osler et al., 2003); the Swedish Conscripts Birth Cohort 1949-51, involving 49,262 men who took mental ability tests at 18 to 20 years and who were followed up for 31

years (Hemmingsson, Melin, Allebeck, & Lundberg, 2006); a cohort of the Vietnam Experience Study (VES) with IQ test scores from the time of military conscription, who were followed up to a mean age of 53 years (Batty, Shipley, Mortensen, Boyle, et al., 2008).

The term "cognitive epidemiology" was first defined by Deary and Der (2005) in the journal *Psychological Science*. A glossary of the field, including a description of common epidemiological and intelligence-related concepts, was published in the *Journal of Epidemiology and Community Health* (Deary & Batty, 2007). In the same year, a systematic review in *Annals of Epidemiology* collected the inverse associations between premorbid IQ and total mortality (Batty, Deary, & Gottfredson, 2007). Overview articles published in the journals *Intelligence* (Deary, 2009; Lubinski, 2009), *Maturitas* (Kilgour, Starr, & Whalley, 2009), and *Nature* (Deary, 2008) summarised research in the field and developed the discussion surrounding potential mechanisms of the intelligence-mortality link. Crucially, a special issue on cognitive epidemiology (Vol. 37, No. 6) was published in *Intelligence* in 2009*,* advancing understanding of issues that have emerged more recently, with articles covering: Mediators along the intelligence-disease pathway including behaviour (Anstey, Low, Christensen, & Sachdev, 2009), medical compliance (Deary, Gale et al., 2009), substance use and abuse (Johnson, Hicks, McGue, & Iacono, 2009); the relation of cognitive ability to specific morbidities such as cardiovascular disease (Singh-Manoux et al., 2009), metabolic syndrome (Richards et al., 2009), and psychiatric health (Gale, Hatch, Batty, & Deary, 2009); the contribution of a 'fitness factor' in understanding underlying causes (Arden, Gottfredson, & Miller, 2009). The main findings of this empirical work are presented following this next section, on epidemiological practices.

Finding roots in epidemiology

A definition of epidemiology is:

> The study of the distribution and determinants of health-related states and events in populations, and the application of this study to control health problems (Last, 1988, p.159)

For cognitive epidemiology to prosper in this context, the disciplines of differential psychology and epidemiology should each aim to establish roots in the other. The field asks that epidemiologists give greater consideration to genetic influences on health inequalities, in balance with established environmental factors (Deary, 2010), and that psychometric intelligence tests, as valid and stable measures of general cognitive ability, are given credence. Conversely, psychologists studying individual differences require understanding of fundamental principles of epidemiology, distinguishing association from causation for one (Rothman & Greenland, 2005), and need to apply them using their variables, if they are to make valid contributions to the field. Such key epidemiological concepts and methods are introduced here, with examples given from cognitive epidemiology. More in depth coverage of these can be found in introductory, (Rothman, 2002) or comprehensive, textbooks (Bhopal, 1997; Hennekens & Buring, 1987).

Causation

Evaluating the evidence that cognitive ability is a direct, or indirect, causal factor for health outcomes is a complex challenge, familiar to epidemiologists who must carefully interpret new associations between risk factors and disease. Sets of guidelines available to observational epidemiology are useful tools in deciding upon whether causation can be reliably deduced. Table 1.1 presents a recent list of six such criteria (Bhopal, 2008), which find their origin in Bradford Hill's (1965) nine "viewpoints", with some credit given to Evans' (1978) "rules of evidence". Here each of these in turn is discussed, with relevance to validating the likelihood of causation in cognitive epidemiology.

1. Temporality

The first criterion, *temporality*, considers if the measure of exposure precedes signs or symptoms of disease and can therefore be conceptualized as a predictor variable. In cognitive epidemiology, the most robust means to evaluate this comes from longitudinal cohort studies that link cognitive ability scores of children or young adults with their medical or mortality records in later adult life. Although general cognitive ability scores show high stability across the life-course (Deary et al., 2000), studies referenced in this chapter's introduction show that onset of certain somatic diseases or their treatments, can result in changes to cognitive function. Therefore, cohorts that are young at the time of IQ testing reduce the risk of reverse causation in studies that evaluate intelligence as a risk factor for disease.

2. Strength

The *strength* of an association is a second guideline, asking whether variation in the exposure is associated with differences in the risk of disease, which would give credence in support of causality. Large population datasets that have full, representative distributions of intelligence are best suited to evaluate this criterion, as are cohorts with longer periods of follow-up that increase the number of disease or mortality cases, ensuring adequate statistical power. Cognitive epidemiology has been fortunate to have such datasets available from several Westernized countries, including Australia, Scandinavia, US and the UK (Batty, Deary, & Gottfredson, 2007). In most cases these have been government initiatives via educational or military institutions. Such sizeable and representative cohorts are quite novel to psychological research, which often draws upon smaller convenience samples, including student populations. Detailed descriptions of many of these cohorts are available elsewhere (Deary & Batty, 2011), but two examples include: The Scottish Mental Surveys of 1932 and 1947 (SMS32 and SMS47) involving mental ability scores from the majority of 11-year-olds who were born in Scotland in 1921 and 1936 respectively, and who were attending schools on specific dates of testing in 1932 and 1947 (see Deary, Whalley & Starr, 2009 for cohort profile). Together these cohorts involve over 150,000 individual children's data, and follow up for health information on subsamples of the cohorts has so far been 69 years. The second

example of a population-based cohort is the Swedish Conscripts Study, including over 1.3 million men with IQ test scores taken at 18 years of age, at entry to national service, representing nearly the entire Swedish male population born during 1950 to 1976 (Batty, Wennerstad, et al., 2007). These data are linked to recent detailed Cause of Death registers from Sweden, and because the maximum age at follow-up is about 50 years at the present time, this cohort will continue to gain in value with the greater number of mortality data. Evidence for the varying strength of the association between intelligence and mortality is discussed later on.

3. Specificity

In support of causation is also the evidence for the *specificity* of an association: Does intelligence relate more strongly to the risk of some diseases over others? Findings from single cohort studies can indicate differences in the risk of particular causes of death associated with mental ability scores. For example, in the Swedish Conscripts study, a one *SD* decrease in IQ was associated with a 31% increased risk of coronary heart disease (CHD)-mortality, a 22% increased risk of accident and suicide-related mortalities, and a 3% increased risk of total cancer deaths by middle-age (Batty, Wennerstad, et al., 2009). However, such findings require replication to support specificity. Evaluation of empirical data on cause-specific outcomes follows in the next section of this chapter.

4. Consistency

A fourth guideline, *consistency*, demands that the association between exposure and outcome be replicated across cohorts of varying time, place and circumstance, if causation is to be inferred (Bradford Hill, 1965). So far, this has been supported by a systematic review of premorbid IQ and all-cause mortality, which reported a significant inverse association across nine cohorts from five different countries (although all Caucasian). Mental ability scores came from a range of intelligence test batteries. Cohort members were born in various decades of the twentieth century, and were either representative of military personnel or, more

broadly, schoolchildren, from their background populations (Batty, Deary, Gottfredson, 2007).

5. Biological plausibility

A *biological* plausibility of the association between premorbid intelligence and morbidity is the most challenging to test of Bradford Hill's criteria. A biological explanation for the intelligence-mortality association is presented by system integrity theory, which implies an underlying complex physiology that determines both cognition and health outcomes; this hypothesis may ultimately be addressed by the field of genetics research. An alternative explanation is that intelligence may act indirectly upon health outcomes, by determining health behaviours and socioeconomic factors in adulthood. These central theories are discussed in the final section of this chapter.

5. Experimental evidence

Experimental evidence for causation is another problematic guideline for the field of cognitive epidemiology to address. However, if a genetic or environmental exposure was identified that naturally showed changes to individuals' intelligence test scores, then exposed versus non-exposed participants of a cohort could theoretically be tested and followed up for the risk of disease.

Real or artefact?

Confounding is a perennial problem in observational epidemiology and must be continuously appraised and tested in order to avoid errors of interpretation. For example, childhood socioeconomic status (SES), commonly indicated by factors such as family income, parental occupation, or education, is often cited as a potential confounder in the association between premorbid intelligence and health. In social epidemiology, childhood SES is studied as an underlying factor of health inequalities within populations, where cognitive resources are largely ignored, or regarded as

mediators of a SES-health phenomenon (Gallo, Espinosa de los Monteros, & Shipuri, 2009; Lleras-Muney, 2005; Bartley & Plewis, 2007). The converse view taken is that intelligence may be the underlying cause of social inequalities in health (Gottfredson, 2004). Whether the contribution of intelligence to health outcomes is a real effect, or an artefact of confounding SES factors, is addressed by cohort studies that contain detailed childhood measures of both variables. Some of this evidence is discussed later.

Measuring risk

Epidemiologists routinely use logistic regression or Cox proportional hazards regression when quantifying the relationship between a variable and disease risk. These methods are appropriate given that the health outcome is nearly always binomial: For example, *disease* or *no disease*; *dead* or *alive*. The odds ratio (*OR*) is the measure of risk probability derived from logistic regression (Cox, 1958), and in epidemiology is the ratio between two likelihoods of a health outcome occurring given a particular exposure, and of the health outcome not occurring given the same exposure. The hazard ratio (*HR*) is a similar proportional measure, derived from Cox proportional hazards regression (Cox, 1972), but is the preferred statistic by epidemiologists (Symons & Moore, 2002) because it takes in to account the time to an event for each individual, rather than assuming that the magnitude of risk is constant in respect of time.

In cognitive epidemiology, when the exposure variable is continuous (e.g., as in IQ-type scores) it can be represented as a unit (per-point) difference, or a one *SD* difference in intelligence scores. The hazard or odds ratio are reported with their 95% confidence interval (CI) giving an indication of the statistical significance of risk. Both effect sizes have null effects at 1, and a confidence interval that includes 1 indicates that there is no statistically significant association between the health outcome (i.e. disease) and the exposure (e.g. IQ) at $p < 0.05$. Conventionally, if the ratio and its CI exceed 1, it indicates a significantly increased risk of disease given a specified *SD* decrease or increase in mental ability scores. Conversely, if an effect

size and its CI fall below 1, this indicates that risk of disease is significantly decreased given the unit change in test scores.

The degree of risk is often reported as a percentage, so that for example, if a *HR* for mortality given a one *SD* increase in IQ is 0.78 this can be expressed as a 22% reduced risk. Alternatively, a *HR* of 1.22 translates as a 22% increase in risk of disease. This expression offers a useful way to interpret the degree of attenuation by covariates, for example when studies report the *HR* before and after adjustment for SES. In understanding the risks generated by such analyses, it is always important to attend to the units of the exposure variable.

Premorbid intelligence and risk of total mortality

A systematic review published in the *Annals of Epidemiology* identified nine unrelated longitudinal cohorts, each one reporting a significant association between lower premorbid intelligence test scores and increased risk of all-cause mortality in adulthood (Batty, Deary, & Gottfredson, 2007). The paper not only helped to validate the IQ-mortality association, but it raised a number of questions for the field to address; for example: What is the size and nature of confounding by early life factors? What extent do adult SES factors mediate the association? Is the magnitude of the association the same for women as for men (most military cohorts were male-only)? And, what is the influence of premorbid cognitive ability on specific causes of death?

There has been a considerable increase in the publication frequency of intelligence versus all-cause mortality studies since the review. This has provided an opportunity to quantify the association using meta-analysis, and to address some of these pertinent issues, which is the subject of the next chapter. The systematic review I present in Chapter 2 involves an electronic search using strict inclusion criteria, to extract longitudinal studies where psychometric intelligence in youth have been associated with all-cause mortality by follow-up in adulthood.

Gender differentials in intelligence-mortality associations

Gender differences in the onset, patterns and prevalence of health behaviours, risk factors, and disease (Anand et al., 2008; Wingard, 1984), might contribute to sex differentials in intelligence-health gradients. The SMS32 cohort was the first study to estimate IQ-mortality effects by sex, reporting a stronger association between childhood IQ and risk of mortality in women (more than double) compared to men (Whalley & Deary, 2001). However, the increased rate of death among high IQ-scoring males during the Second World War may have reduced the effect size for men in this particular cohort. The UK's National Survey of Health and Development (NSHD) study provided a more recent birth cohort, born in 1946, with cognitive scores at age 8 and followed up age 54. This study reported that, among male members with low cognitive scores, there was twice the risk of mortality compared to high scorers, whereas no effect was observed for women (Kuh, Richards, Hardy, Butterworth, & Wadsworth, 2004). However, the increased life expectancy of women compared to men, which reduces the relative number of female to male deaths, may have lost statistical power to this study. Indeed, in a more recent follow-up of the same British cohort, with an increased number of female deaths, the effect became significant; that is, women scoring in the highest quartile for cognitive ability had a 51% reduced risk of mortality by follow-up, compared to those in the lowest quartile (Kuh et al., 2009). The meta-analysis in Chapter 2 reports on the aggregate effect sizes for the IQ-mortality association for men and women separately, to address the potential sex differential.

Dose-response effects on all-cause mortality

Studies that report on the risk of mortality according to a one *SD* difference in IQ-type scores assume a linear association. However, exploration of incremental effects on the intelligence-mortality slope could reveal a threshold beyond which an association no longer exists. The afore-described study of the 1946 cohort provided evidence that premorbid cognitive ability is only predictive of risk of death at the low end of the range for cognitive ability. Men who scored in the bottom quartile of the cognitive score distribution were reported to be at nearly twice the risk of mortality

compared to those scoring in the top quartile, whereas there were no statistically significant differences in risk of mortality between the second, third and top quartile groups (Kuh et al., 2004). After adjusting for educational attainment or adult SES the effect was removed, suggesting that the influence of cognitive ability on mortality might be mediated by adverse socioeconomic factors more common among low scorers (or that intelligence is a causal factor in these outcomes, as well as in health). Two further studies have also supported a threshold effect of cognitive ability on risk of all-cause mortality above the lower end of the IQ distribution (Hart et al., 2003; Hemmingsson et al., 2006). However, a US study of gifted children, with Stanford-Binet IQ scores in the high range (135 to 163), reported a 32% decreased risk of mortality given one *SD* increase in IQ (Martin & Kubzansky, 2005), evidence that, even at the highest end of the IQ distribution, an intelligence-mortality gradient is observed. Furthermore, three population-representative cohorts support this (Batty, Wennerstad, et al., 2009; Osler et al., 2003; Whalley & Deary, 2001), ruling out the possibility that the effect is driven by specific health problems associated with learning disabilities (Batty & Deary, 2004). In a single study, over a million Swedish conscripts were divided evenly in to nine groups of ascending intelligence scores and a monotonic (linear) relationship was observed between IQ and risk of mortality (Batty, Wennerstad, et al., 2009). This is shown in the time-to-survival curve in Figure 1.2. This evidence emphasises the importance of a whole-population approach to understanding mechanisms relating premorbid intelligence to premature mortality.

g or specific cognitive function?

Despite the use of different cognitive ability test batteries among cohort studies used in cognitive epidemiology, including the Moray House Test, Wechsler Adult Intelligence Scale, Stanford-Binet, and Raven's Progressive Matrices tests (Deary and Batty, 2007), the magnitude of the associations between their global IQ-type scores and risk of all-cause mortality show relative consistency. It is likely therefore that the general intelligence factor (*g*), which accounts for up to half of the total variance in batteries of diverse mental ability tests' scores (Carroll, 1993), is a better cognitive predictor of health outcomes than measures of specific cognitive

function. In the Swedish Cohort Study performance scores on four cognitive tests including verbal reasoning, visuospatial ability, logical reasoning and technical ability, were each inversely associated with all-cause mortality to the same magnitude as that of a global cognitive score (Batty, Wennerstad, et al., 2009). However, among follow-up studies that have estimated the risk of mortality according to specific cognitive function measured in adulthood, a steeper gradient has been reported for fluid compared to crystallized intelligence (Batterham, Christensen, & Mackinnon, 2009), and a significant inverse association was shown for executive function but not for verbal and visuospatial reasoning abilities (Hall, Dubin, Crossley, Holmqvist, & D'Arcy, 2009). Still, until further cohort data of specific cognitive abilities in childhood become available, the issue remains as to whether specific cognitive function could relate differentially to health outcomes.

One alternative indicator of cognitive function that has been measured in childhood, and that could help to explain mechanisms underlying associations with health outcomes, is processing speed. Reaction time tasks, which measure information processing efficiency, have been significantly associated with all-cause mortality, in that faster reaction times are associated with reduced risk (Deary & Der, 2005). In this UK adult cohort of 898 members, reaction time also very substantially attenuated the association between IQ and all-cause mortality after 14 years' follow up. This finding lends support to the system integrity theory (Whalley & Deary, 2001) of intelligence's associations with health outcomes, if processing speed is an effective indicator of neurological integrity which reflects overall physiological integrity. In Chapters 6 and 7 the Twenty-07 cohort is used to investigate associations between reaction time performances and CVD biomarkers measured after 20-year follow-up.

Other psychological traits in cognitive epidemiology

Intelligence measures remain the strongest and most consistent predictors of death in differential psychology, and yet behaviour traits such as personality may also be important risk factors for adult mortality, either independently or in

interaction with intelligence. In the SMS47 6-Day Sample 1,181 children who had IQ scores at age 11, and teacher-rated personality ratings at age 14, were followed-up for a period of 55 years for all-cause mortality (Deary, Batty, Pattie, & Gale, 2008). A *dependability* factor extracted from item scores measuring perseverance, conscientiousness, and stability of mood, was significantly associated with the reduced risk of death by follow-up. Furthermore, mortality risk was twice as great for children who scored in the bottom half of the IQ and dependability distributions, compared to those in the top half of those distributions. High scores on a *neuroticism* factor among US military conscripts were also significantly related to an increased risk of mortality (Weiss, Gale, Batty, & Deary, 2009). Neuroticism showed independent effects from IQ score in predicting risk of death, but an interaction effect was also reported; that is, the effect of intelligence on mortality was more pronounced at high levels of neuroticism, and, the effect of neuroticism on mortality was more pronounced at low levels of intelligence.

More recently, a delinquency factor measured by the Minnesota Multiphasic Personality Inventory was associated with the risk of mortality at age 75, after controlling for the influences of education and IQ (Trumbetta, Seltzer, Gottesman, & McIntyre, 2010). However in this analysis, mean imputation was applied to a quarter of participants with missing IQ data, which may have weakened the effect of IQ in the model, particularly if missing cases were at the lower end of the distribution.

Specific causes of morbidity and mortality

A single theoretical basis for the intelligence association with total mortality is unlikely, given that causes of death vary so widely. For example, IQ's association with risk of accidental injury (a leading cause of mortality in early adulthood) may not be explained by the same mechanism relating it to the risk of coronary heart disease (the main cause of death in Westernised countries by middle age). Unless it was shown that intelligence reflects a general propensity to look after one's self in the short and longer terms. Many cohorts relevant to cognitive epidemiology have linked to death records that include specific causes of death, or medical or hospital

admission records that contain information on specific morbidities. In this section, empirical studies of the association between intelligence and specific causes of mortality and morbidity are reviewed, and the behavioural and psychological risk factors along these pathways are discussed.

Cardiovascular disease

The higher incidence of cardiovascular disease (CVD)-related deaths compared to other causes of death in midlife has enabled several longitudinal studies to explore its risk according to premorbid intelligence. The first empirical data were from Scotland: 938 participants from the 1972 Midspan prospective cohort studies, whose IQ scores at age 11 were available from 1932, were followed up for a period of 25 years, by which time 43% had a CVD-related outcome (Hart et al., 2004). In this group a 15-point decrease in IQ was related to 11% increased risk of hospital admission or death due to CVD, with the risk increasing further for those events occurring up to 65 years (22%). Similar inverse associations for premorbid intelligence and risk of CVD diagnosis or death have been replicated by other well-characterised cohorts, including: The SMS47 6-Day Sample (Deary, Whiteman, Starr, Whalley, & Fox, 2004), and the Swedish Conscripts Study 1940-51 in which data on nearly 50,000 men were collected (Hemmingsson et al., 2006). Coronary Heart Disease (CHD) and stroke are the most common causes of CVD-related deaths but albeit sharing some modifiable risk factors, they differ in their pathogeneses. It is therefore important to consider how intelligence might relate to each of these morbidities separately.

Coronary heart disease

In respect to risk of CHD outcomes the magnitude of the association with premorbid intelligence has been fairly consistent. The Midspan study by Hart et al. (2004) has been the longest follow-up study for CHD outcomes, reporting a 16% increased risk of CHD-related hospital admission or death according to a one *SD* decrease in IQ. This increased to a 29% risk once CHD events occurring above age

65 were excluded. Further cohorts, with follow-up to midlife, report similar findings. The Danish Metropolit study of 6,910 men born in 1953 in Copenhagen, obtained IQ test scores from 12 years, and traced cause-of-death and hospital discharge records to age 47 (Batty, Mortensen, Andersen, et al., 2005). Relative to the highest IQ scoring quartile, the lowest, second and third quartile groups had an increased risk of 170%, 143% and 69%, respectively, for CHD events. These effects were little changed after adjusting for early life factors, including birth weight and childhood SES. In a similar cohort design, the Aberdeen Children of the 1950s study of 11,125 members reported a 30% reduced risk of fatal or non-fatal CHD according to a one *SD* advantage in intelligence (Lawlor, Batty, Clark, Macintyre, & Leon, 2008). The risk of CHD in association with intelligence test scores was greater in women (51%) than in men (21%), and was also shown to be incremental when hazard ratios were calculated separately for eight groups of increasing IQ test score. However, after adjusting for education, the effects reduced to non-significance. The Swedish Conscripts study also reported attenuating effects of education on a 31% increased risk of CHD-mortality according to a one *SD* decrease in IQ, although this was by 45% only, and the effect remained statistically significant (Batty, Wennerstad, et al., 2009). In this study adjustment for early-life and physical factors including birth year, parental social class, BMI, blood pressure, and illness, made little change to the association between mental ability scores and risk of CHD-related death.

Stroke

Studies of the association between premorbid intelligence and stroke have not been so definitive. This may be because the trend for an inverse association has not reached statistical significance in some cohorts (Batty, Mortensen, Andersen, et al., 2005; Hart et al., 2004), owing to the lack of power from low numbers of stroke events. However, in a sufficiently large study - the Aberdeen Children of the 1950s - a one *SD* advantage in intelligence was significantly associated with a 32% reduced risk of incident stroke (Lawlor et al., 2008), an effect which increased for women compared to men. Furthermore, the Swedish Conscripts cohort was large enough to estimate effects of premorbid intelligence on risk of stroke subtype. The authors

reported inverse associations for all fatal and non-fatal stroke events, for each subtype, which were statistically significant in most cases (Wennerstad, Silventoinen, Tynelius, Bergman, & Rasmussen, 2009). However, the strongest association was estimated for hemorrhagic strokes, and there was a weaker effect for ischaemic strokes. Adjusting for childhood SES, BMI and systolic blood pressure, or education, only modestly attenuated these effects.

CVD risk factors

Established risk factors for CVD include diabetes mellitus, obesity or overweight, metabolic syndrome, and hypertension. If pathways between intelligence and cardiovascular outcomes are to be understood, then it is important to evaluate cognitive ability in relation to each of these. Among 7,476 men and women from the US National Longitudinal Survey of Youth (1979), with intelligence test scores from adolescence, a one *SD* increase in mental ability scores was associated with the significantly reduced odds of self-reported hypertension (16%), heart problems (16%) and diabetes (12%) at age 40 (Der, Batty, & Deary, 2009). Hypertension was also associated with childhood cognitive ability in the SMS32-Midspan cohort. Among 938 men and women a one *SD* increase in IQ was associated with a 3.15 mmHg reduction in systolic blood pressure and a 1.5 mmHg reduction in diastolic blood pressure (Starr et al., 2004).

Metabolic syndrome

Metabolic syndrome is characterised by a cluster of cardiovascular-risk factors including abdominal obesity, high blood pressure, high blood triglycerides, low HDL cholesterol, and hyperglycaemia. Data from the VES reported that premorbid intelligence scores were inversely associated with four out of five risk factors measured at midlife, including blood triglycerides, blood pressure, blood glucose and BMI. By adjusting for these, the risk of mortality from CVD according to IQ scores was attenuated by about a third. In the NSHD 1946, study a one *SD* advantage in IQ at age eight years was associated with a 14% reduced odds of

metabolic syndrome at 53 years of age (Richards et al., 2009). Of all the metabolic syndrome risk factors, lower IQ was most strongly associated with high blood pressure, blood triglycerides and abdominal obesity. Education or adult income attenuated the size of risk to non-significance, one interpretation of which is an indirect effect of cognitive ability on this cluster of risk factors. The inverse relationship between childhood IQ and risk of obesity and weight gain in midlife was also significant, according to data on nearly 10,000 men and women from the 1958 National Child Development Study (Chandola, Deary, Blane, & Batty, 2006). This study reported a stronger effect of risk of obesity in women (38%) than men (26%) according to a one *SD* difference in IQ, and all effects were attenuated to non-significance after adjusting for educational attainment.

Emerging CVD biomarkers

More recent work has begun to investigate the association between intelligence and emerging biomarkers for CVD. For example, one study reported that lower childhood cognitive ability was significantly associated with increased levels of C-reactive protein (CRP) and fibrinogen in blood samples taken between 67 and 71 years of age (Luciano, Marioni, Gow, Starr, & Deary, 2009). Both are inflammatory markers that are frequently raised in patients with vascular diseases. An understanding of the mechanisms underlying the relation between cognitive ability and biomarkers of disease is warranted, in particular whether premorbid intelligence leads to health behaviours that increase inflammatory components of cells, or, whether inflammatory processes are an aspect of system integrity that underlie individual differences in intelligence. These questions are addressed to some extent in Chapters 5 and 6 of this thesis.

Other cause-specific morbidities in cognitive epidemiology

Cancers

Given that cancers share some common modifiable risk factors with CVD, including obesity and smoking, it might be expected that the association between premorbid intelligence and cancer morbidities are consistent with those for CVD. However, the evidence to date does not support this. The Swedish Conscripts Study of nearly one million men reported a non-significant 3% increased risk of total cancer mortality according to a one *SD* decrease in IQ (Batty, Wennerstad, et al., 2009). Similar negligible findings were reported from the earlier Swedish Conscripts Study (1949-51 birth cohort) that reported an increased risk of 4% for a one *SD* decrease in IQ (Hemmingsson et al., 2006), and the SMS32-Midspan cohort that reported a 8% increased risk of all-cancer-morality given the same unit change in IQ (Hart et al., 2003). However, one large U.S. military cohort has estimated a significant inverse relationship between IQ and risk of all-cancer mortality. Data from the Vietnam Experience Study, in which IQ scores were available for 14,491 male conscripts at an average age of 20 years, were linked to cancer-mortality records up to middle age. A 27% increase in risk of all-cancer mortality was reported according to a one *SD* decrease in IQ (Batty, Mortensen, et al., 2009). This may be due to IQ's association with specific cancers, as the risk was found particularly high for smoking-related cancer deaths (an increased risk of 37%).

Given the many different types of cancers, with multiple causes and risk factors, it has been appropriate to look at the effects of IQ in relation to specific types of cancers, rather than treating them as a homogenous disease group. Hart et al. (2003) reported a 36% increased risk of lung cancer associated with a one *SD* decrease in IQ, and a 46% increased risk in stomach cancer, although this failed to reach a level of statistical significance because of the small number of cases. No effects were observed for colorectal or breast cancers, but again larger cohorts would be required to achieve adequate statistical power. By far the largest study found statistically significant weak associations between intelligence and carcinoma of stomach (where any protective effect of intelligence was seen only in the highest intelligence tertile), but not lung or other cancer death; it also found that high intelligence was a risk factor for skin cancer (Batty, Wennerstad, et al., 2007). This latter effect may be due to the relation between higher intelligence and job income, and the resulting increased frequency of holidays spent in hot climates, although it

was only slightly attenuated after controlling for SES, and remained significant. It is possible that negative health behaviours such as smoking and poor diets may help understand mechanisms underlying IQ's relation to particular malignancies. Future cohort studies with larger numbers of specific-cancer cases are required to evaluate this properly.

Respiratory disease

Given the inverse association between IQ and smoking and the positive association between IQ and smoking cessation uptake (Batty, Deary, & Macintyre, 2007; Batty, Deary, Schoon, & Gale, 2007c; Taylor et al., 2003), it is perhaps unsurprising that higher premorbid IQ is also associated with the reduced risk of illnesses relating to respiratory function in adult life. For example, the NLSY79 cohort reported a 22% reduced odds of developing chronic lung disease at age 40, according to a one *SD* increase in intelligence test scores (Der et al., 2009). Furthermore, two studies have demonstrated a significant association between childhood mental ability and improved lung capacity, based on forced expiratory volume (Deary, Whalley, Batty, & Starr, 2006; Richards, Strachan, Hardy, Kuh, & Wadsworth, 2005). This observation may be explained by IQ being positively related to height, and, by dint of their bodily habitus, taller people having high lung function, which may indicate a general fitness factor underlying the link between cognitive ability and these physical markers; however, in one study the positive association remained statistically significant after controlling for adult height in addition to birth weight, adult SES and lifetime smoking (Richards et al., 2005).

Intentional and unintentional injury

Unintentional injury or death can be the result of road traffic or industrial accidents, or falls for example. In the Danish Metropolit study higher childhood cognitive scores of 11,339 males were associated with a 22% reduced risk of fatal or nonfatal injury by road traffic accidents, falls or unintentional poisoning, by 48 years of age (Osler, Andersen, Laursen, & Lawlor, 2007). The effects of IQ on risk of

falling and poisoning were still significant after adjusting for educational status. IQ exposure was also inversely related to injury mortality among over one million Swedish men (Batty, Gale, et al., 2009). Low IQ scorers compared to the highest IQ scorers had a 482% increased risk of death by poisoning, a 339% increased risk of fire mortality, 217% increased risk of fall mortality, 216% higher risk of drowning, and a 117% increased risk of road injury mortality. The inverse association between cognitive ability and injury mortality was incremental across the IQ range, and SES inequalities explained about half of the total effects.

The association between premorbid intelligence and accidental injury is consistently higher than that seen for chronic disease. However, this may only be the case for serious injuries that lead to hospitalisations or death. Studies that assess cognitive ability in relation to minor accidents or injuries can be complicated by problems of self-reporting. This may have affected differences in self-recall by participants from the British birth cohort of 1970, in which higher childhood cognitive scores were related to the increased reporting of accidents in the home by age 30 (Batty, Deary, Schoon, & Gale, 2007a).

Intentional injury or death can be self-inflicted, for example attempted suicide, or it can be the result of others' actions, including physical attack and homicide. Due to the low numbers of suicide and homicide cases in cohorts, only very large studies ensure sufficient statistical power with which to evaluate their associations with premorbid intelligence. A cross-sectional ecological study of census data from 48 European and Asian countries had reported a positive association between mean literacy rates and incidence of suicide among older adults, in that, the higher the literacy rate, the greater the incidence of suicide (Voracek, 2005). However, such study design fails to take account of individual differences and changes in populations over time. Published in the same year, longitudinal data from the Swedish Conscripts Study reported a significant inverse association between premorbid intelligence test scores and risk of death by suicide up to midlife (Gunnell, Magnusson, & Rasmussen, 2005). The authors suggested that lower cognitive ability might contribute to an increased risk of suicide either because it is a risk factor for psychiatric illness, or because of a disadvantage in being able to resolve problems or personal crises. Within the same cohort Batty, Deary, Tengstrom, and Rasmussen

(2008) related the Swedish conscripts' IQ scores to homicide mortality after twenty years of follow-up. A one *SD* increase in premorbid IQ was associated with a 51% reduced risk of death by homicide, and the effect was incremental across the IQ range. This effect was marginally attenuated by early life social factors, height, and somatic and psychiatric illness. Explanations for this finding included: People with higher IQ scores being more able to negotiate and resolve conflicts, or having a higher perception of risk; lower IQ scorers being more frequently intoxicated with alcohol or drugs; an association between the intelligence of perpetrator and victim (perpetrators of homicide have lower than average IQ scores) (Batty, Deary, Tengstrom, et al., 2008). Another explanation is the confounding influence of height, which, as described, has been positively associated with cognition (Gale, 2005; Vågerö & Modin, 2006), and may be protective against the threat of external physical attack (Batty, Deary, Tengstrom, et al., 2008). These potential explanations deviate from the mechanistic pathways posited for other cause-specific mortalities highlighting the need to evaluate multiple mechanistic models for intelligence and morbidity pathways.

Behavioural risk factors for disease

Tobacco smoking, excessive alcohol consumption and sedentary living are risk factors common to a range of life-threatening diseases, including CVD, which as reported above, shows some of the strongest and most consistent associations with premorbid intelligence. Longitudinal cohorts have been used to evaluate associations between premorbid mental ability and these health behaviours, to explore how they might explain IQ-mortality pathways.

Cigarette smoking

Higher childhood intelligence is positively associated with a reduced risk of current or previous cigarette smoking in adults (Batty, Deary, Schoon, et al., 2007c; Taylor et al., 2003), an effect which is attenuated by educational attainment, and to a lesser degree adult SES (Batty, Deary, Schoon, et al., 2007c). In two UK studies

smoking cessation in adulthood was more likely among higher childhood intelligence test scorers, particularly women (Batty, Deary, Schoon, et al., 2007c), and controlling for deprivation index attenuated the effect (Taylor et al., 2003). However, in the Swedish Conscripts Study (1949 to 1951), IQ was not associated with quitting smoking (Hemmingsson, Kriebel, Melin, Allebeck, & Lundberg, 2008). Members of this study would have been exposed to public health promotions of the 1970s to reduce smoking, at a younger age than cohort members of the previous two studies. This could suggest that higher intelligence leads to more adaptive behaviours, in response to new public health campaigns (Taylor et al., 2003).

Alcohol consumption

The association between childhood IQ scores and excess alcohol consumption in adulthood is less consistent than for smoking. In a Scottish cohort born in the 1950s, assessed for IQ at age 11, and followed up with alcohol-related questionnaires at age 44 to 53, there was a significant inverse relationship between childhood IQ and self-reported hangovers (Batty, Deary, & Macintyre, 2006). For one *SD* increase in IQ there was a 20% reduced odds of having regular alcohol-related hangovers in midlife – an indicator of regular binge drinking – that was attenuated after controlling for adult SES. However, in a different study from Denmark, a null association was reported between IQ and excess drinking in men (Mortensen, Sørensen, & Grønbæk, 2005). Furthermore, two studies have indicated that intelligence can positively correlate with excess alcohol consumption. Data on men and women from the NSHD 1946, including childhood cognitive scores from age 8, and self-assessment of alcohol abuse at age 53, reported that those whose cognitive scores were in the top half of the distribution, were at 2.4 times the odds for alcohol abuse (Hatch et al., 2007). A second British cohort of men and women born in 1970, with cognitive scores at 10 years, and information on alcohol use at age 30, reported that higher intelligence was positively related to increased regular intake of alcohol, as well as perceived alcohol problems (Batty, Deary, Schoon, et al. 2008). This association was stronger for women, and remained significant after controlling for education and social factors. Attrition or response bias could be causing these

positive findings, but further studies are warranted to better understanding alcohol drinking behaviours (including participants' choice of alcohol type) that are influenced by cognitive ability differences.

Lifestyle

Childhood cognitive ability has also been related to taking more physical exercise, consuming more healthy foods (including fruit, vegetables and wholemeal bread) and less unhealthy foods (chips, cakes and biscuits), and vegetarianism, which could also mediate intelligence-disease pathways (Batty, Deary, Schoon, & Gale, 2007b; Gale, Deary, Schoon, & Batty, 2007). More well characterised cohorts with detailed information on exercise and nutritional lifetime habits are required in order to understand their contribution to IQ-disease associations.

Psychiatric illness

Mental health problems are also important to consider in cognitive epidemiology, because they pose greater health risks to individuals, are enduring throughout the life course, and lead to increased risk of comorbidities and mortality. For example, psychiatric illness is linked to more negative health behaviours, including smoking (Lawrence, Mitrou, & Zubrick, 2009), and is a risk factor for suicidal behaviour (Moscicki, 1995) and cardiovascular disease (Phillips et al., 2009; Van der Kooy et al., 2007). Large well-characterised cohort studies consistently show an inverse association between premorbid intelligence and risk of mental health problems, as characterised in Table 1.2. In Scotland and Denmark lower cognitive scores were associated with the increased likelihood of presenting with a psychiatric disorder over long-term follow-up (Batty, Mortensen, & Osler, 2005; Walker, McConville, Hunter, Deary, & Whalley, 2002). Furthermore, in cohorts from New Zealand, Sweden and US the association was significant for a range of specific psychiatric diagnoses, including anxiety-related disorders, depression and schizophrenia, by middle age (Gale, Batty, Tynelius, Deary, & Rasmussen, 2010; Gale et al., 2008) or younger (Koenen et al., 2009). For example, among over one

million men from the Swedish Conscripts Study, lower IQ scores were associated with a greater risk of hospitalization for eight psychiatric disorders by midlife (Gale et al., 2010). These included a 60% increased risk of being admitted for schizophrenia, a 50% increased risk for mood disorders, and a 75% increased risk of alcohol-related disorders, associated with a one *SD* decrease in IQ scores. In the VES cohort, intelligence was inversely related to the risk of alcohol disorders, depression, generalized anxiety disorder, and post-traumatic stress disorder (Gale et al., 2008), and the magnitude of these risks increased if more than one disorder was present, so that the likelihood of psychiatric comorbidity increased as participants moved towards the lower end of the IQ distribution.

At the less extreme end of psychiatric illness, higher cognitive ability at age 10 and 11 is also related to a reduced risk of self-reported psychological distress in early adulthood, according to a combined cohort of over 12,000 members from the 1958 National Child Development Survey and the 1970 British Birth Cohort (Gale, Hatch et al., 2009). Adjusting for early life factors and SES in childhood and adulthood made no difference to this effect, but the inclusion of education in the model showed moderate attenuation.

Pathological cognitive decline and dementia

Lower premorbid intelligence is also associated with the risk of later pathological cognitive decline. A sample from the SMS32 cohort reported the inverse association with risk of late-onset, but not early-onset, dementia (Whalley et al., 2000). A larger sample of the SMS32 enabled late-onset dementia cases to be separated into vascular dementia and Alzheimer's type dementia, in evaluating associations with premorbid cognitive ability. The investigators reported that lower childhood intelligence was a significant risk factor for late-onset vascular dementia, but not Alzheimer's, suggesting that vascular processes rather than cognitive reserve are likely mediators in the pathway between early life intelligence and later cognitive decline (McGurn, Deary, & Starr, 2008). Whether this suggests an underlying biological mechanism consistent with system integrity theory, or can be explained by risk behaviours that damage vascular health, is an issue for future investigation.

An important point about this observation, in the context of this thesis, is that it highlights the potential for reverse causation in cognitive ageing studies that may infer a directional pathway only from pathological disease to cognitive decline. The field of cognitive epidemiology can therefore highlight the likelihood of reverse causation in disease specific cases, by understanding pathways from premorbid cognition to later health outcomes. Reverse causation is a subject for empirical study in Chapters 5 to 7 of this thesis.

Intelligence to disease mechanisms

The growing body of empirical studies reflected in this chapter has advanced the understanding of the likely mechanistic pathways that relate individual differences in cognitive ability scores to disease outcomes and death. Deary (2008) reflected that there is as yet "no clear chain of causation from intelligence to health" (p.176). It is, however, likely that intelligence differences may play an important role as risk factor, mediator, and covariate in models that explain health outcomes. It could also prove to be a partial confounder for other early life or social factors. A mechanistic model for the associations between IQ and mortality (from Batty, Deary, & Gottfredson, 2007), based on earlier theoretical suggestions of Whalley and Deary (2001), is shown in Figure 1.3, indicating most of these possibilities. Additional to the model is the more explicit recognition of the potential contribution of genetic factors that underlie both individual differences in intelligence and health, which are yet to be adequately explored (Arden, Gottfredson, & Miller, 2009). The theory of system integrity, present in the model, posits that an underlying physiological make-up may explain the association between premorbid intelligence and health outcomes. Molecular genetics studies are required to directly test this theory, which is out with the present thesis. However, the plausibility of system integrity may be tested indirectly using indicators for an underlying trait, such as reaction times as mentioned above. Progress in cognitive epidemiology has been made in some pathways of this illustrated model more than others. The empirical evidence for the role of social and behavioural influences is presented next.

Social and environmental factors: Causation or mediation?

It is an ongoing debate whether intelligence or socioeconomic status (SES), makes the greater contribution in predicting health outcomes of populations (Bartley & Plewis, 2007; Gallo et al., 2009; Gottfredson, 2004). In social epidemiology, common indicators of SES are education, occupational income or social class (Hackman & Farah, 2008), and advantages in these have been associated with lower risk of total or cause-specific mortality, and health morbidities, in longitudinal cohort studies (DeWalt, Berkman, Sheridan, Lohr, & Pignone, 2004; Huisman et al., 2005; Lleras-Muney, 2005; Singh-Manoux, Ferrie, Chandola, & Marmot, 2004; Torssander & Erikson, 2010) - although evidence suggests that these are not interchangeable factors for a latent social trait (Geyer, Hemstrom, Peter, & Vågerö, 2006; Torssander & Erikson, 2010). The issue is made more complex by the covariation between cognitive ability and socioeconomic indicators (Lubinski, 2009). Causal associations between intelligence and SES are obscured and controlling for either IQ or SES when evaluating the other's relation to mortality can "weed out some of the very influence… we are trying to detect" (Deary, 2008, p.176).

Confounding by social inequalities

One theory is that early life influences, particularly SES, are total confounders of the association between premorbid mental ability and adult morbidities. The evidence so far suggests that controlling for parental occupational status in early life has little effect on the IQ-mortality effect size (Batty, Deary, & Gottfredson, 2007). One study that controlled for an alternative childhood SES factor - overcrowding in the home - also showed negligible attenuation of the IQ-mortality link (Whalley & Deary, 2001). This also seems to be the trend in studies reported in the previous section of this chapter assessing specific morbidities in relation to premorbid cognition. However, the role of confounding by socioeconomic inequality requires formal testing, which is another subject of the next chapter.

Other potential early life confounding

It has been posited that adverse events in the prenatal period or early childhood such as exposure to smoking, and obesity, which are not captured by common indices of SES, may yet explain some of the association between premorbid cognitive function and adult health outcomes (Kilgour et al., 2009), but data for such an idea are as yet unavailable. A study of young infants who were adopted within the first year of life, reported an inverse association between their adult mortality rates and the social class of their biological father, whereas a null association was found with risk of mortality and the adoptive fathers' social class (Osler, Peterson, Prescott, Teasdale, & Sørensen, 2006). This suggests that genetic factors more likely explain the intelligence-mortality link, unless environmental factors that carry their influence in the very early stages of development remain unaccounted for. So far, studies that have controlled for birth weight (an indicator of prenatal events) have reported negligible attenuation of the association between intelligence and mortality (Jokela, Elovainio, Singh-Manoux, & Kivimaki, 2009; Leon, Lawlor, Clark, Batty, & Macintyre, 2009; Osler et al., 2003), although this may not be surprising given that correlations between birth weight and childhood cognitive ability are modest (Shenkin, Starr, & Deary, 2004). Future cohort studies of more detailed early life measures, including maternal factors, would help clarify whether IQ-type scores may act in part as a surrogate for early life determinants of health.

Mediation by adult socioeconomic attainment

Adult SES indicators may explain more of the influence of cognitive ability scores on health outcomes. It is well established that higher childhood mental ability is predictive of better educational and socioeconomic successes (Deary, Strand et al., 2007; Schmidt & Hunter, 2004; Strenze, 2007; Von Stumm, Macintyre, Batty, Clark, & Deary, 2010; Zagorsky, 2007). These can lead to a "protective chain of events" for long life (Batty & Deary, 2004, p.586): Better working conditions in higher-ranking jobs provide safer and healthier environments; more comfortable, less hazardous home environments afforded by increased incomes; educational and/or occupational

successes leading to improved heath literacy and the means to better understand medical advice and intervention, and greater exposure to accurate public health knowledge with which to engage. In the meta-analysis of Chapter 2, one question addressed is the effect of adjusting for adult socioeconomic status on the IQ-all-cause mortality effect. It is noted among studies that have simultaneously controlled for occupational status and education, the association between premorbid intelligence and all-cause mortality has entirely diminished (Kuh et al., 2009: Jokela, Batty, Deary, Gale, & Kivimaki, 2009; Jokela, Elovainio, et al., 2009). Home ownership has also been shown to have a significant attenuation effect on the risk of mortality according to intelligence test scores (Kuh et al., 2009). However, due to these variables often strongly positively correlating, with each other and with intelligence test scores, there is the risk of statistical overadjustment when simultaneously controlling for their effects in epidemiological models.

Adjustment for cognition in SES-mortality models

An alternative way of evaluating intelligence along with SES in respect of health outcomes has been to assess the potential attenuating effects of cognitive ability in relations between social inequalities and health outcomes. This helps test the theory that intelligence is the fundamental cause of social inequalities in health, as posited by Gottfredson (2004). In the west of Scotland Twenty-07 study, respective risks of CHD-related and total mortalities according to five child and adult SES indices were estimated, before and after adjusting for adult IQ scores (Batty, Der, Macintyre, & Deary, 2006). In support of 'fundamental cause' theory, controlling for intelligence scores entirely attenuated the inverse associations between years in education and the risk of CHD-related and total mortality (by 111% and 131% respectively), as well as the inverse association between adult SES and risk for these mortalities (94% and 106% respectively). However, for other SES indices intelligence had less of an attenuating effect, reducing by about a third-to-a-half the effects of childhood SES, income and deprivation on CHD and total-mortality outcomes. Other health measures including respiratory function, long-term illness and poor self-perceived health also saw varying attenuation effects by IQ

scores in this study, and it was reported that low SES was still significantly predictive of some poor health outcomes after adjusting for intelligence in adulthood. In the Swedish Malmo cohort, where intelligence test scores were measured in childhood, these were not found to fully explain social inequalities in health outcomes although marked attenuation was apparent. Adjusting for IQ reduced the education-mortality gradient by only one quarter in men, and the size of the effect actually increased in women following controlling for cognitive ability (Lager, Bremberg, & Vågerö, 2009). The association between IQ and risk of mortality was neither entirely explained by childhood SES or education, suggesting that intelligence has independent effects on health outcomes from those of SES.

A note on statistical overadjustment

It is possible that attenuation effects observed in these studies may be caused by overadjustment (Deary & Batty, 2007), rather than mediation or confounding. A challenge for cognitive epidemiology is to separate these influences. Structural equation modelling (SEM) provides one means by which to do this, as it at least controls for covariation. One paper to use SEM analyses, presented alongside standard regression, used the Vietnam Experience Study data, and reported that the effect of IQ was entirely mediated by education, income and poor physical health, and had no direct effects on risk of mortality (Weiss et al., 2009). However, this evidence cannot rule out the possibility that education acts as a proxy for intelligence. To consider the potential overadjustment by controlling for education in IQ-mortality models, Chapters 3 and 4 employ a novel behaviour-genetics method applied to two whole-population samples, to investigate the extent to which heritability accounts for the significant phenotypic association between these two variables.

Disease management and health behaviour

It is likely that individual differences in lifetime patterns of health behaviours and self-care management are on the pathway between premorbid cognitive ability

and health outcomes, yet the extent of their mediation effects are not yet established. Although these are considered here separately, they are certainly not exclusive of socioeconomic factors and education but have strong associations in their effects on the IQ-mortality link. Indeed they may more accurately reflect the social and behavioural influences that interplay with cognitive processes, thereby affecting health outcomes.

Self-management in population health

Self-management of disease and treatment intervention is a cognitive undertaking (Gottfredson, 2004). Better health outcomes are more likely if people are able to understand and remember medical advice and instruction during the course of disease, if they can plan and execute necessary changes in their lifestyle to facilitate disease management or recovery, and if they recognise earlier on symptoms that are likely to necessitate further medical intervention. Within clinical populations cognitive ability has been positively associated with correctly following medical regimens. In female patient groups with diabetes, breast cancer and hyperlipidemia, better cognitive performance on memory, attention and executive function tasks, were associated with greater compliance with medication dosages (Stilley, Bender, Dunbar-Jacob, Sereika, and Ryan, 2010). Furthermore, in a randomised placebo-controlled trial of patients with atherosclerosis, verbal intelligence in adulthood was positively related to continuing with medication two years after treatment allocation (Deary, Gale et al., 2009). Those scoring in the lowest quartile for the verbal test were 2.5 times more likely to have stopped medication within two years, compared to those in the highest quartile group. Among ageing populations of many industrialised countries, it is recognised that patients may be increasingly burdened with a life-long involvement in their own complex disease management, the success of which may depend on effective cognitive processes (Gottfredson, 2004). So far in cognitive epidemiology however, the extent to which disease management mediates intelligence-morbidity associations has been unexplored, due to the lack of such descriptive variables in longitudinal cohorts with premorbid cognitive test scores. Therefore this remains a pertinent area for the field to address.

Mediation by health behaviours

Health behaviours are also integral to disease management or prevention. In the previous section of this chapter, associations between premorbid cognitive ability and health behaviours were discussed. However there is little evidence so far that such behaviours account for the link between mental ability, and morbidity or mortality. For example, in the Vietnam Experience Study the 29% reduced risk of all-cause mortality according to a one *SD* increase in IQ, was attenuated by 7% to 14% after separately adjusting for alcohol consumption and smoking (Batty, Shipley, Mortensen, Boyle, et al., 2008). Furthermore, cognitive performance is sometimes more strongly predictive of risk of mortality relative to behavioural risk factors, suggesting that these cannot account for the intelligence-mortality link. Cognitive function, as measured using choice reaction time, was observed to be a stronger risk factor for CVD mortality, than smoking, alcohol consumption and physical exercise, in the UK Health and Lifestyle Survey (Roberts, Der, Deary, & Batty, 2009). In the Twenty-07 study childhood cognitive ability was more strongly associated with all-cause mortality than all established risk factors for CVD, with the exception of smoking (Batty, Deary, Benzeval, & Der, 2010). If health behaviours do account for some of the inverse association between intelligence and risk of disease or mortality, then their effects are likely to vary according to cultural and historical contexts. In industrialised countries for example, where health behaviours and lifestyle may be playing a role in epidemics of chronic diseases, their mediation effects may be greater (Gottfredson, 2004).

System integrity

The theory of general body integrity posits that the inverse association between premorbid cognitive ability and health outcomes may be explained by underlying physiological make-up (Whalley & Deary, 2001). In this context, childhood mental ability is an early indicator of system integrity and therefore a covariate with risk of disease rather than a causal factor acting upon it. This theory

finds resonance with the field of cognitive ageing in which some empirical data show physical and cognitive deterioration acting in parallel (Deary, 2008). However, it presents challenges in its testing particularly as indicators for system integrity remain imperfect.

Cognitive processing speed

One putative marker for system integrity adopted by the field is reaction time, a measure of cognitive processing efficiency that may reflect neurological as well as general bodily integrity (Batty & Deary, 2004). Not only is faster reaction time significantly correlated with higher cognitive test scores (Neisser et al., 1996), it is associated with the reduced risk of CHD, CVD, respiratory disease, lung-cancer, digestive-related and all-cause mortalities (Gallacher et al., 2009; Roberts et al., 2009; Shipley, Der, Taylor, & Deary, 2006). As mentioned earlier, the Twenty-07 study reported that reaction time largely attenuated the inverse association between cognitive ability and all-cause mortality (Deary & Der, 2005), providing support for the system integrity theory. Another marker of system integrity is physical coordination, as measured by childhood upper and lower limb-related tasks. However, despite significant associations with both IQ and health outcomes, this indicator does not appear to explain the intelligence-mortality association (Gale, Batty, Cooper, & Deary, 2009).

Alternative indicators for underlying system integrity

Other potential markers of system integrity that positively correlate with mental ability scores, include low morning cortisol peaks (Power, Li, & Hertzman, 2008), semen quality (Arden, Gottfredson, Miller, & Pierce, 2009), and indices of physical health that might indicate a 'fitness factor', including cranial, motor and peripheral sensory nerves, reflexes, head and general physical health (Arden, Gottfredson, & Miller, 2009). It remains to be seen whether these contribute to an understanding of the intelligence-mortality relation. A major contribution to testing this particular theory is likely to come from future genetics research. One relevant

study has identified a molecular genetic linkage between lower cognitive ability and a marker for inflammation, vagal tone (Frye, 2009). Reduced vagal nerve signalling is associated with an increased risk of total mortality, CVD, type 2-diabetes, metabolic syndrome, and depression, and so may yet provide evidence for a system integrity theory of the IQ-mortality association, in which inflammatory processes could underlie neurological and physiological integrity.

Summary

The empirical work in this thesis addresses some key questions in cognitive epidemiology, highlighted in this chapter, including the nature of the association between intelligence and education (Chapters 3 and 4)—relating to the issue of overadjusted models in predicting health outcomes, and, the social and mediating pathways linking premorbid cognition to preclinical CVD risk (Chapters 5 to 7). First however, Chapter 2 formally tests the magnitude of effect linking premorbid intelligence to all-cause mortality, including a statistical review of confounding and mediation by socioeconomic factors that may help to explain this replicated finding.

Table 1.1 Six epidemiological questions for assessing likelihood of causation

Causation guideline	Question
Temporality	Does the proposed causal factor precede the effect?
Strength	Does exposure variation influence incidence of outcome?
Specificity	Does the exposure relate more strongly to some outcomes over others?
Consistency	Is the association replicated between and within studies?
Experiment	Does altering exposure to the cause influence incidence?
Biological	Is the association biologically plausible?

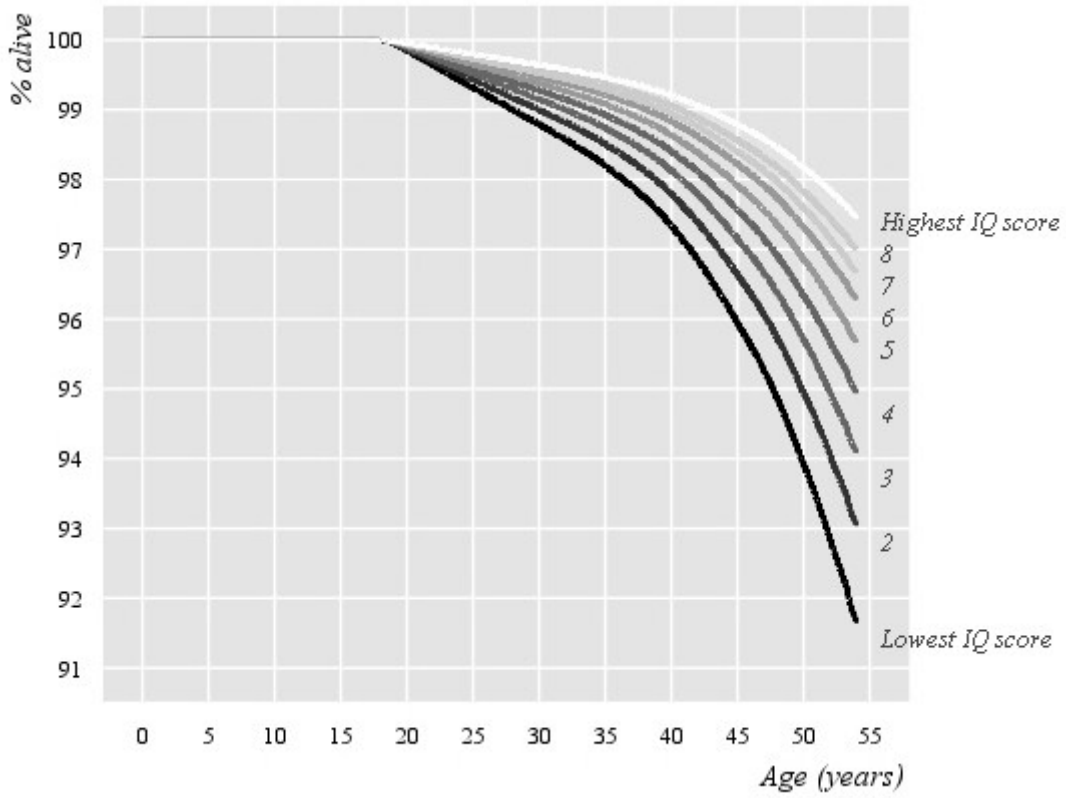
Note. The list of guidelines originated from Bradford Hill, A. (1965). The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine*, *58*, 295-300, with distillation by Bhopal, R. (2008). *Concepts of Epidemiology*: *Integrating the Ideas, Theories, Principles and Methods of Epidemiology*, *Second Edition*. Oxford University Press.

Table 1.2 Summary of longitudinal studies on premorbid cognitive ability and adult mental health outcomes.

Study	Citation	Age at cognitive testing, yr	Age at follow-up, yr	Cohort *N*		Psychiatric outcome
SMS32	Walker et al., 2002	11	76	4,99	↑	Any psychiatric disorder
Danish cohort	Batty, Mortensen, & Osler, 2005	12	49	7,022	↑	Any psychiatric disorder
NCDS58	Gale, Hatch, et al., 2009	10	33	6,369	↑↑	Psychological distress
BCS70	Gale, Hatch, et al., 2009	11	30	6,074	↑	Psychological distress
VES	Gale et al., 2008	20	midlife	3,258	↑ ↑ ↑↑ ↑	Alcohol-related disorder Depression GAD PTSD
Dunedin cohort	Koenen et al., 2009	11	32	1,037	↑ ↑ ↑↑ ↑↑	Depression GAD Schizophrenia Social phobia
Swedish Conscripts	Gale et al., 2010	18	midlife	1,049,663	↑↑ ↑↑ ↑↑ ↑↑ ↑↑ ↑↑↑ ↑↑ ↑↑↑	Adjustment disorder Alcohol-related disorder Mood disorder Neurotic disorder Non-affective psychosis Personality disorder Schizophrenia Substance-use disorder

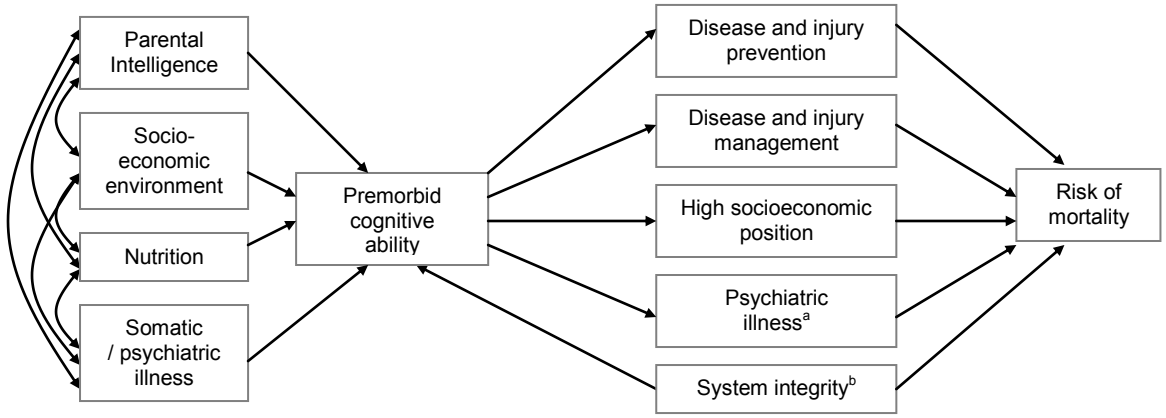
Note. Arrows indicate the magnitude of effect, which here represents a significantly increased risk of a psychiatric outcome, per one standard deviation decrease in cognitive ability: ↑ indicates 10% to 39% increased risk; ↑↑ 40% to 69% increased risk; ↑↑↑ 70% or more increased risk. SMS32 = Scottish Mental Surveys 1932; NCDS58 = National Child Development Study 1958; BCS70 = British Cohort Study 1970; VES = Vietnam Experience Study; GAD = Generalized Anxiety Disorder; PTSD = Post-traumatic stress disorder.

Figure 1.1 Survival rates from 18 to 54 years per IQ score (1-9), among 1,133,712 Swedish men.



Note. Compiled with permission from F. Rasmussen using the Swedish Cohort data described in Batty, G. D., Wennerstad, K. M, Davey Smith, G., Gunnell, G., Deary, I. J., Tynelius, P., & Rasmussen, F. (2007). IQ in early adulthood and later cancer risk: Cohort study of 1 million Swedish men. *Annals of Oncology*, *18*, 21-28.

Figure 1.2 Model of influences on premorbid IQ, and potential pathways to mortality.



Note. Reproduced and revised with permission from: 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.

[a] Although psychiatric disease is shown as a possible mediating variable between IQ and mortality, it might also be an antecedent variable if, for example, suboptimal neurodevelopment were the prior cause of both psychiatric disease and early mortality.

[b] System integrity is shown as antecedent to both IQ and mortality. In this pathway, lower IQ is not a cause of mortality, but both IQ and mortality are influenced by this more fundamental physiological integrity. Double-pointed arrows indicate correlations between antecedent variable.

Chapter 2
Intelligence in youth and all-cause mortality: Systematic review with meta-analysis

Introduction

As described in Chapter 1, individual differences in intelligence test scores, as measured by standardized IQ-type tests in childhood, show an inverse association with risk of death from all causes throughout adulthood. That is, higher intelligence appears to confer protection. This finding is replicated in prospective cohorts from several Westernized countries (Batty, Deary, & Gottfredson, 2007) across different ranges of intelligence (Leon et al., 2009) and in follow-up periods from early through to late adulthood (Batty, Wennerstad, et al., 2009; Hart et al., 2003; Leon et al., 2009). Intelligence and somatic health may be inextricably linked throughout the life course. However, longitudinal studies help to establish causal pathway models of the effects of one upon the other. For example, morbidities such as diabetes, cancer, stroke and peripheral atherosclerosis, and/or their treatments, are reported to cause a decline in cognitive function after longitudinal follow-up (Arvanitikas, Wilson, & Bennett, 2006; Comijs et al., 2009; Kivipelto et al., 2005; Okereke et al., 2008; Rafnsson, Deary, Smith, Whiteman, & Fowkes, 2007; Yaffe et al., 2004). This illness-to-cognitive ability direction of association is a commonplace finding. The reverse direction of association is studied less often, and has only recently come to be recognized under the term "cognitive epidemiology" (Deary & Batty, 2007; Deary & Der, 2005). That is, mental ability scores from early life associated with later adulthood morbidities, and before any somatic symptoms or risk factors of disease are manifest, provide evidence that cognitive abilities may be predictive of later health outcomes. The association between premorbid intelligence and adult all-cause mortality was the subject of a systematic review (Batty, Deary, & Gottfredson, 2007), in which all nine studies that met the inclusion criteria demonstrated an inverse relationship between intelligence and risk of dying by the time of follow-up.

The review did not quantify the association. Furthermore, there were insufficient studies to address comprehensively a number of pertinent questions from this research domain.

Sex differential effects

One issue is whether or not the association between intelligence and mortality is the same in women as in men. For example, it is possible that sex differences in the incidence, age at onset of health behaviours, and the extent to which these act as risk factors for disease (Anand et al., 2008; Schenck-Gustafsson, 2009), could produce sex-specific intelligence–mortality gradients. Data from many more men than women have been included in intelligence–mortality cohort studies to date, mainly due to some studies using military conscript databases. Moreover, when mixed-sex cohorts report mortality risk as predicted by intelligence for men and women separately, they rarely test for statistical difference but, rather, report the observed trend. With more studies now reporting hazard ratios for mortality by sex, there is an opportunity to quantify the predictive effects of intelligence on mortality separately for men and women.

Confounding by early social influences

A second issue yet to be evaluated systematically is the extent to which intelligence as a predictor of mortality is confounded by early-life environmental influences including socioeconomic factors. Socioeconomic status (SES) is established as an important determinant of public health inequalities (Davey Smith & Lynch, 2004; Gallo, Espinosa de los Monteros, & Shivpuri, 2009; Macintyre, 1998; Marmot, 2010), including risk of mortality, and it can carry influence in childhood, via factors such as family income and parental education, to predict individual differences in childhood intelligence (Lawlor et al., 2005; McLoyd, 1998). In this context, therefore, intelligence may be considered a mediating variable on the pathway between early-life influences and adult health outcomes. If early social factors substantially confound the link between intelligence and longevity, then

adjusting for childhood SES would sizeably attenuate the effect size of the association between intelligence and mortality. In their systematic review, Batty, Deary and Gottfredson (2007) identified three out of nine studies that adjusted for childhood SES: One of these showed no change from an unadjusted model, and two had modest attenuating effects, suggesting that intelligence has independent effects on risk of mortality from those of early socioeconomic influences. Due to this small number of studies, the role of childhood SES in the intelligence–mortality link requires further investigation.

Mediation by attained socioeconomic status

One explanation why intelligence may exert an influence on life expectancy is its ability to predict educational outcomes (Deary, Strand, et al., 2007) and occupational class (Schmidt & Hunter, 2004), which can both affect health outcomes via a number of mechanisms; for example, the knowledge and living conditions that contribute to risk exposure, health behaviours, and self-management (Evans & Kim, 2010; Stringhini et al., 2010). In population studies these adult SES factors are themselves inversely associated with risk of mortality (DeWalt et al., 2004; Huisman et al., 2005; Lleras-Muney, 2005). Some prospective cohorts take account of the attenuating effects of education and adult SES in estimating the risk of mortality according to intelligence; yet, to date, their influence has not been properly evaluated.

The present study

Investigators are giving increasing attention to the issues raised here, with a higher rate of publications reporting risk estimates for all-cause mortality according to differences in intelligence since the first systematic review (Batty, Deary, & Gottfredson, 2007). There is now an opportunity to re-evaluate this augmented literature, this time with a quantitative, meta-analytic approach. The systematic review from 2007 reported the overall quality of the nine studies as “moderate”, which was in part related to the weak validity of some measures of premorbid

intelligence. Therefore, one important change to the systematic process reported here is the inclusion of studies in which only valid cognitive assessments were used. Kilgour et al. (2009) also raised a number of methodological considerations that should be addressed in intelligence–mortality studies, including taking account of ascertainment bias, age, sex and education. In this article I will address the influence of these factors using subgroup analyses. Accordingly, the aims of this chapter are to:

- Quantify the association between premorbid intelligence and all-cause mortality.
- Determine whether there are sex differences in the association.
- Conduct subgroup analyses on studies that adjust for early-life SES, adult SES and education, to discover their magnitude of influence as potential confounders or mediators of the intelligence–mortality association.

Methods

Systematic review process

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

'Mortality risk' or 'Mortality*' or 'Mortality trends'), an asterisk allowing the search term to precede a longer word or phrase.

The electronic search conducted on 5th February 2010 yielded 19,236 articles. Two reviewers (N. Leckenby and I) independently scanned each title and abstract, retrieving articles on the basis of their relevance to intelligence and mortality. We applied the inclusion criteria listed below to these respective shortlists of papers. I then examined the reference lists of the selected articles, along with review papers on intelligence and mortality, and my own personal files (my supervisors checked their own), for articles that the electronic search might have missed. Among the final list of articles, when more than one paper reported intelligence–mortality associations from the same cohort, thereby duplicating data, it was agreed between myself and my supervisors, which papers would be retained, according to criteria of the following order: 1) The article reported the hazard ratio for mortality per one *SD* difference in IQ-type score; 2) The cohort size was larger; 3) The article was the original publication to report the data.

Inclusion criteria

I included published cohort data that fulfilled criteria similar to that of the previous systematic review on intelligence and all-cause mortality (Batty, Deary, & Gottfredson, 2007). First, to minimize risk of reverse causality, only cohorts where intelligence test score data were collected at a mean age of 24 years or younger were included (the period classified as childhood and youth according to the World Health Organisation Study Group (WHO Study Group, 1990)). Second, the intelligence and mortality data were collected at the level of the individual. Third, the relationship between intelligence and all-cause mortality was reported quantitatively. Furthermore it was also stipulated that the premorbid test should demonstrate an acceptable degree of validity as a measure of intelligence. Finally, the cohort was excluded if it had been selected from a clinical or unrepresentative population.

Statistical analysis

The *HR* with 95% CI for all-cause mortality per *SD* advantage in intelligence test score was the principal outcome variable. For hazard ratios expressed per one *SD* disadvantage in intelligence, the reciprocal was used. Reported odds ratios were treated as hazard ratios, with the caveat that these effect estimates approximate one another (Greenland, 1987) when the incidence of an event (e.g. mortality) is low (Symons & Moore, 2002). In case–control studies reporting intelligence test means for living and deceased, the standardized mean difference was converted to an *OR* using formulae by Chinn (2000). Authors were contacted if it was not possible to derive an effect size from their published data. Fixed effects models were assumed for the aggregation of hazard ratios based on evidence of a low degree of heterogeneity, where $p < 0.10$ (Sutton et al., 2000). Subgroup analyses were conducted by sex group, for those studies to adjust for SES variables, and by study characteristic groupings for the purposes of sensitivity analysis.

MIX 1.5 (Bax, Yu, Ikeda, Tsurata, & Moons, 2006) was used for all analyses and production of plots. The inverse variance method was used to weight study effect sizes.

Sensitivity analyses

Sensitivity analyses aggregated effect sizes by the following study characteristics: Ascertainment rate at follow-up; age at intelligence testing; cohort size; duration of follow-up; average birth year of the cohort; effect size measure (see Table 2.2 for group parameters).

Ascertainment rate may bias the intelligence–mortality effect size if those who emigrate, and are therefore excluded from follow-up, differ on cognitive ability scores compared with those who remain within geographical regions for census. Follow-up rates were estimated based on the proportion of participants from the original cohort that were followed up and included in the final analyses, regardless of whether or not intelligence test scores were available for them. Studies were grouped on the basis of <80% or 80–100% ascertainment rates.

Studies were also aggregated according to age at cognitive testing, first because the likelihood of an effect of bodily insults on intellectual function increases

with age and, with it, the risk of reverse causation bias in the intelligence– mortality link. Conversely, the validity of cognitive testing may be greater in older cohorts, and these may reflect more homogeneous results compared with results of younger children at intelligence testing for whom there is more measurement error.

For the duration of follow-up, studies were divided on the basis of a median split of the years traced for mortality. Although there may be stronger grounds for assuming causality as the time period between intelligence testing and mortality increases, there is also evidence that, by older adulthood, the intelligence–mortality association loses significance (Hart et al., 2005).

The reason for aggregating studies that reported either hazard ratios or odds ratios was to ensure that the treatment of these measures of association did not inflate the overall effect size.

Studies were also grouped according to cohort size and decade of birth, as these may also have influenced heterogeneity across the studies. However, it was decided not to aggregate for population representativeness as one of our criteria ensured the exclusion of clinical samples. Nevertheless, due to two study cohorts being less representative of the general population (twins and gifted children) than all others, meta-analytic results are reported with and without their effect sizes (Holsinger, Helms, & Plassman, 2007; Martin & Kubzansky, 2005).

Publication bias

Inspection of a funnel plot was used to assess publication bias, with standard error on the *y*-axis as recommended by Sterne and Egger (2001). Publication bias was further evaluated with Egger's test of asymmetry, and trim-and-fill adjustment methods.

Results

Systematic retrieval of studies

The electronic search resulted in 19,236 publications and, of these, the independent review process extracted shortlists of 73 and 69 relevant articles respectively (<0.4% of total publications), from which 90 nonduplicate publications were retrieved for closer inspection (see Figure 2.1 for review process). Among these 64 failed to meet one or more inclusion criteria (see Appendix A for full reference list and reasons for exclusion). A further three studies that met inclusion criteria were identified from the reference lists of the remaining 26 papers, or from review articles or personal records (Deary, Whalley, & Starr, 2003; Furu, Lingarde, Ljung, Munck, & Kristenson, 1984; Link, Phelan, Miech, & Westin, 2008). Two out of 29 studies were excluded (Furu et al., 1984; Link et al., 2008) because insufficient data were obtainable to calculate the intelligence–mortality effect sizes. (Table 2.1 lists the characteristics of the final 27 studies). I excluded 11 articles from the meta-analysis because they overlapped with cohort data of another report (Hart et al., 2005; Deary, Whalley, & Starr, 2003; Batty, Gale, et al., 2008; Batty, Mortensen, Gale, & Deary, 2008; Batty, Shipley, Gale, Mortensen, & Deary, 2008; Deary, Whiteman, Starr, Whalley, & Fox, 2004; Hemmingsson, Melin, Allebeck, & Lundberg, 2009; Kuh et al., 2004; Starr, Deary, & Whalley, 2008; Vagero & Modin, 2006; Weiss et al., 2009). Justification for excluding these data were: 1) The overlapping reports of a sample were generally reported by the same research group resulting in consistent methods of sample selection and data linkage; and, 2) the majority of overlapping cohorts were of similar size and follow-up duration.

Study descriptions for meta-analysis

Sixteen prospective longitudinal cohort studies included 22,453 deaths among 1,107,022 participants (see Appendix B for references). These were from five countries; UK (n = 7), USA (n = 5), Sweden (n = 2), Australia (n = 1) and Denmark (n = 1), ranging in size from 862 to 994,262 participants. Figure 2.2 illustrates these variables according to year of publication, showing a trend for larger cohorts accumulating in more recent years. Premorbid intelligence test scores were taken from school records (n = 10), military or national service conscription records (n = 5), or a research database (n = 1). The average age at testing ranged from 7 to 20

years, and length of follow-up ranged from 17 to 69 years. Six cohorts were all male (five from conscription databases), and the remainder were mixed sex.

Cognitive Assessments

A range of cognitive assessments were used across studies, and evidence was sought of their validity as standardized measures of intelligence. The concurrent or predictive validity of five tests used across nine of the study cohorts (Batty, Wennerstad, et al., 2009; Hart et al., 2003; Holsinger et al., 2007; Hemmingsson et al., 2006; Jokela, Batty, et al., 2009; Kuh et al., 2009; Lager, Bremberg, & Vagero, 2009; O'Toole et al., 1988; Whalley & Deary, 2001) have been reported elsewhere (Batty, Deary, & Gottfredson, 2007). Here the evidence for psychometric validity among the seven remaining cohorts is described:

- The Binet and Stanford-Binet tests used in two studies (Martin & Kubzansky, 2005; Deary, Batty, Pattie, et al., 2008) are well-established, age-standardized intelligence tests for children. Scores on the original Stanford–Binet test contain a single underlying factor of cognitive ability (Wright, 1939) and the Binet scale has concurrent validity with version 12 of the Moray House intelligence test (r = 0.80) (Deary, Batty, Pattie, et al., 2008).
- Two studies included selected tests from the well-validated Moray House series (Thomson, 1940). The first study incorporated Moray House tests 57 and 58 in an 11-plus examination that also assessed language and arithmetic (Pearce, Deary, Young, & Parker, 2006). On this exam, total scores have shown well-established associations with childhood height at ages 9 and 13 years (Pearce, Deary, Young, & Parker, 2005). The second (Leon et al., 2009) used Moray House Picture Tests 1 and 2, which have also shown expected patterns of association with intrauterine and childhood growth (Lawlor et al., 2005).
- The Harnquist test used in the Danish Metropolit study (Osler et al., 2003) has shown concurrent validity: A general intelligence factor extracted from scores on the test at age 13 years strongly positively

correlated (r = 0.78) with a military classification intelligence test taken five years later (Härnqvist, 1968).

- The Armed Forces Qualification Test (AFQT) used in another study (Jokela, Elovainio, et al., 2009) strongly correlates with other well-validated IQ tests (median r with seven tests = 0.81), and scores on the four subtests show high loadings on a single g factor, from 0.81 to 0.87 (Hernstein & Murray, 1994).
- Finally, the Vietnam Experience Study (Batty, Shipley, Mortensen, Boyle, et al., 2008) used the Army General Technical test, which strongly correlates with verbal reasoning (r = 0.75) and visuospatial (r = 0.51) scores from the Weschler Adult Intelligence Scale (WAIS), a standardized and well-validated cognitive ability test battery.

Mortality records

Records of mortality were ascertained prospectively in seven studies, either by linkage of study members to national register databases (Hart et al., 2003; Holsinger et al., 2007; Jokela, Batty, et al., 2009; Kuh et al., 2009; Pearce et al., 2006) or by individual follow-up with study participants or their families (Martin & Kubzansky, 2005; Jokela, Elovainio, et al., 2009). In the remaining studies, incidence of death was ascertained retrospectively by access to national death registers—in Swedish cohorts record linkage used personal identification numbers rather than person names (Batty, Wennerstad, et al., 2009; Hemmingsson et al., 2006; Lager, Bremberg, & Vagero, 2009)—with the exception of two studies that did not report methods for extracting death records (O'Toole et al., 1988; Batty, Shipley, Mortensen, Boyle, et al., 2008). Ten papers estimated the intelligence–mortality effect size as a hazard ratio with confidence intervals (see Table 2.2 for citations of these papers), two used odds ratios or logistic regression coefficients (Jokela, Batty, et al., 2009; Jokela, Elovainio, et al., 2009) and two reported the M and SD which I converted to an estimated OR (Holsinger et al., 2007; O'Toole et al., 1988). In response to email requests authors of the two further papers provided hazard ratios

(Kuh et al., 2009; Osler et al., 2003), as these were unreported in the original publications.

Intelligence–mortality meta-analysis: Basic model

In the basic model, a *HR* from each of the 16 studies was either, unadjusted (*n* = 2), adjusted for age (*n* = 3), adjusted for sex (*n* = 3), adjusted for age and sex (*n* = 3), or unspecified (*n* = 5) (Table 2.1). However, there was a low degree of heterogeneity between the effect sizes of these models (Q = 17.7, I^2 = 15.5%, p = 0.28).

In a fixed effects model, a one *SD* advantage in intelligence was associated with the lower risk of all-cause mortality (*HR* 0.76, 95% CI 0.75 to 0.77) (Figure 2.3 shows this data in a forest plot). The exclusion of two studies (Holsinger et al., 2007; Martin & Kubzansky, 2005) based on selected samples (twins and gifted children) did not alter this estimate; neither did the exclusion of two studies that reported odds ratios and where incidence of death was between 20% and 40% (Holsinger et al., 2007; O'Toole et al., 1988) (data not shown). The statistical weight of the largest study (Batty, Wennerstad, et al., 2009) was 70.5%; excluding this cohort from the model made a negligible change to the effect of intelligence on risk of mortality (*HR* 0.77, 95% CI 0.75 to 0.80).

Sensitivity analysis

Sensitivity analyses results are presented in Table 2.2. Age at intelligence testing may have had a small effect in predicting the risk of mortality. Aggregation of studies in which premorbid intelligence was tested at an average age of between 7 and 12 years resulted in a small attenuation (16%) of the risk of mortality (*HR* 0.79, 95% CI 0.76 to 0.82) compared with that of 18- to 20-year-olds (*HR* 0.75, 95% CI 0.74 to 0.77).

Studies of longer follow-up (40 to 69 years) showed a 20% attenuation of the risk of mortality as predicted by a one *SD* advantage in intelligence (*HR* 0.80, 95% CI 0.76 to 0.83), compared with those cohorts of shorter follow-up (*HR* 0.75, 95% CI

0.74 to 0.77). Furthermore, there was a trend for cohorts born in the 1910s and 1920s to show an attenuated effect size compared with those cohorts born in the 1930 to 1960s. However, these older age cohorts were also those with a longer duration of follow-up.

Ascertainment bias was unlikely to have affected the total aggregate *HR*. That is, studies of low ascertainment (62% to 79%) showed a similar aggregate effect size (*HR* 0.76, 95% CI 0.75 to 0.78) to that of studies with 80% to 100% ascertainment (*HR* 0.77, 95% CI 0.74 to 0.80).

There was also no observable effect of cohort size on the magnitude of the intelligence–mortality association.

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

Publication bias

Examination of the funnel plot revealed only one study (Hart et al., 2003) on the outside of 95% CI parameters (Figure 2.4). Egger's test of asymmetry supported a low risk of publication bias (Intercept = 0.10, 95% CI 0.72 to 0.91, $p = 0.81$), as did application of trim and fill adjustments in which only one missing study was estimated, and its imputation made no difference to the magnitude of the risk estimate (*HR* 0.76, 95% CI 0.75 to 0.78).

Stratification by sex group

Seven studies reported intelligence–mortality effect sizes for men and women separately, and their follow-up spanned 24 to 65 years (Table 2.2 includes these studies' citations). During this period the absolute risk of death was 5.6% for women and 8.2% for men. Four out of the seven studies reported negligible sex differences

(Leon et al., 2009; Jokela, Batty, et al., 2009; Kuh et al., 2009; Jokela, Elovainio, et al., 2009) (two of these formally tested Intelligence x Sex interaction effects), two reported a stronger effect for men (one reported a null effect in women with an intelligence-sex interaction effect) (Lager, Bremberg, & Vagero, 2009; Pearce et al., 2006) and one reported a stronger effect in women (Whalley & Deary, 2001). However, fixed effects models were applied to aggregate the sex-specific HRs, given the evidence for low heterogeneity (Table 2.2). A one *SD* advantage in intelligence among women was associated with a 22% lower risk of all-cause mortality (*HR* 0.78, 95% CI 0.73 to 0.84), whereas among men there was a 20% reduced risk of mortality per one *SD* advantage in intelligence (*HR* 0.80, 95% CI 0.76 to 0.85). Nevertheless, there was a high degree of overlap in the confidence intervals of these respective effect sizes. Egger's test of asymmetry supported a lack of publication bias among sex-specific cohorts.

Adjustment for childhood SES

Nine studies that included 18,733 deaths, reported effect-size models adjusted for childhood SES, measured either by father's occupation or income (Deary, Batty, et al., 2008; Hemmingsson et al., 2006; Jokela, Batty et al., 2009; Leon et al., 2009; Martin & Kubzansky, 2005; Osler et al., 2003; Pearce et al., 2006), the highest socioeconomic index recorded for either parent (Batty, Wennerstad, et al., 2009), or father's education (Lager, Bremberg, & Vagero, 2009). Heterogeneity was very low in unadjusted (Q = 8.56, I^2 = 6.6%, p = 0.38) and adjusted models (Q = 7.49, I^2 = 0.0%, p = 0.48).

In a fixed effect basic model the *HR* for this subgroup of papers did not deviate from that for the 16 studies (*HR* 0.76, 95% CI 0.75 to 0.77). However, even after adjustment for childhood SES there was a very small attenuation (by 4%) of the effect size (*HR* 0.77, 95% CI 0.75 to 0.79) (Figure 2.5). Excluding the large study of over one million Swedish men had no effect on the aggregate effect size of the childhood SES-adjusted model, except to slightly widen the 95% CI parameters (*HR* 0.77, 95% CI 0.74 to 0.80). Compared with the unadjusted model of this smaller group of studies in which there were 4,608 deaths (*HR* 0.77, 95% CI 0.74 to 0.80),

controlling for childhood SES had no effect on the intelligence–mortality gradient when the influence of this largest weighted study was removed. A tenth publication (Kuh et al., 2004) from the systematic review, which could not be included in meta-analysis, reported data consistent with this finding; early-life socioeconomic inequalities did little to explain the inverse association between intelligence and all cause-mortality.

Controlling for adult SES and education

There was no evidence for publication bias among studies that controlled for adult SES or education. In five studies that adjusted for adult SES, there were 3,070 deaths among 66,301 participants. SES was measured either by occupational social class (Hart et al., 2003; Hemmingsson et al., 2006; Jokela, Batty, et al., 2009; Deary, Batty, et al., 2008) or income (Batty, Shipley, Mortensen, Boyle, et al., 2008). The unadjusted effect size for this subgroup of studies (*HR* 0.76, 95% CI 0.72 to 0.79) matched that of all 16 studies. After adjustment for adulthood SES, the lower risk of mortality predicted by higher intelligence was attenuated by 33.5% from the basic model (*HR* 0.84, 95% CI 0.78 to 0.90) (Figure 2.5).

Among the six studies that adjusted for educational attainment, there were 16,023 deaths out of 1,026,742 participants. Again, the aggregate effect size for this subgroup of studies in an unadjusted model (*HR* 0.76, 95% CI 0.74 to 0.77) was no different from that for all 16 studies. After adjustment for education (*HR* 0.89, 95% CI 0.86 to 0.91), the effect of intelligence on mortality was reduced by 54.2% (Figure 2.5). Exclusion of the large Swedish cohort (Batty, Wennerstad, et al., 2009) from the model, as expected, widened the CI parameters (*HR* 0.87, 95% CI 0.81 to 0.93), but still reduced the intelligence–mortality gradient by 45.8% from the unadjusted model. Two further studies from the systematic review (Hemmingsson et al., 2009; Kuh et al., 2004), excluded from meta-analysis due to the type of statistics reported, are consistent with our result. They observed attenuation effects by education of over one third, of the intelligence–mortality association.

Multiple covariates

Eleven studies, including 15,148 deaths, reported effect sizes for the risk of mortality according to intelligence while adjusting for multiple variables (#s 3, 5, 7, 11-12, 14-15 in Appendix A; see Table 2.1 for covariates). Among these cohorts, four showed entire attenuation of the intelligence–mortality effect size from unadjusted (or basic) models (Jokela, Batty, et al., 2009; Kuh et al., 2009; Jokela, Elovainio et al., 2009; Batty, Shipley, Mortensen, Boyle, et al., 2008). These studies tended to adjust for adult SES variables with the addition of other important covariates, including education (Jokela, Elovainio et al., 2009) or smoking (Kuh et al., 2009) among other CVD risk factors (Jokela, Batty, et al., 2009; Batty, Shipley, Mortensen, Boyle, et al., 2008). The remaining studies reported a smaller degree of attenuation from unadjusted models. Due to the varying number and nature of covariates across the studies it was not appropriate to aggregate their effect sizes in meta-analyses.

Discussion

The present meta-analysis of 16 published prospective cohort studies, comprising over 1.1 million participants and 22,453 deaths, demonstrates and quantifies the consistently-reported association between higher premorbid intelligence and lower mortality risk. A one *SD* advantage in intelligence in childhood and youth was associated with a 24% lower risk of mortality. The effect was similar in men and women, and was not explained by socioeconomic differences in early life, as indicated by parental occupation or income. The association was attenuated by approximately a third after adjusting for adult SES and by approximately a half after adjusting for educational experience. Intelligence remained a predictor of mortality after these attenuating effects, and removal of one study that carried by far the largest weighting in the models (Batty, Wennerstad, et al., 2009) did little to change the magnitude of these effects.

This is the first meta-analysis of studies examining the relationship between premorbid intelligence and all-cause mortality. A recent systematic review, which was based on nine identified at that time, reported the inverse association (Batty,

Deary, & Gottfredson, 2007). Since then the number of publications of the intelligence–mortality association has grown, and the 16 unrelated cohorts identified represent more than four times as many deaths. There was little evidence of publication bias, and so the estimated risk of mortality according to a one *SD* advantage in intelligence may be generalized to cohorts beyond those included in this meta-analysis, at least to those of the five countries included in the analyses. My treatment of odds ratios as hazard ratios in two studies where the absolute risk of death was 45%, which could have incurred statistical error, was not found to inflate the aggregate effect size.

Heterogeneity was not apparent across the studies despite most using different assessments of premorbid intelligence. This may be because most omnibus intelligence tests of the types used in the identified studies show strong loadings on a general intelligence factor, or *g* (Carroll, 1993). The intelligence–mortality association was, however, slightly weaker among cohorts of younger ages at cognitive testing, and those of longer follow-up duration. As it was the same cohorts that were followed up beyond 40 years who were the youngest at intelligence testing, it is difficult to establish which factor would make the larger contribution to attenuating the intelligence–mortality association. However, it seems less likely to have been due to differences in the validity of intelligence tests taken at younger and older ages, given the equally low heterogeneity among these two cohort groupings. It may be that older cohorts at cognitive testing show a steeper intelligence–mortality gradient because of the increased likelihood of bodily insults, or, it is still possible that the association varies according to age at mortality, most likely due to cause of death.

Lack of confounding by sex and SES at birth

The observation of negligible differences between men and women in the relative risk of mortality as predicted by intelligence may be surprising given well-documented sex differences in patterns of risk factors, onset and prevalence of specific diseases and life expectancies (Wingard, 1984). However, there were exceptions in individual studies, with differences between men and women reported,

although there seem to be cohort-specific explanations for these. In one study (Whalley & Deary, 2001) the lower relative risk among men was probably due to the rise in deaths of higher intelligence servicemen during World War II (Corley, Crang, & Deary, 2009). In another, the lower relative risk among women could have resulted from a lack of statistical power due to the small number of female deaths (Pearce et al., 2006). The result from an older birth cohort study (Lager, Bremberg, & Vagero, 2009) of a null association among women could have been influenced by a relatively higher incidence of smoking among well-educated women during an era before the health hazards of smoking were widely known. In general, however, data from large post-war birth cohort studies show negligible sex differences in the effects of intelligence in relation to risk of mortality, and results from the meta-analyses support this. Equivalent effect sizes by sex still do not mean that the mechanisms that explain the intelligence–mortality association act in equal measure for men and women, and it continues to be of interest to study sex differences in cognitive epidemiology. Differences in health behaviours, risk patterns and medical interventions should also be considered when comparing ethnic groups or diverse countries. However, there is currently a lack of cohort data to evaluate how such group differences influence the risk of all-cause mortality as predicted by premorbid intelligence.

Socioeconomic conditions in early life, determined by parental occupation or income, were also unlikely confounders. Individual differences in cognitive ability appear to act independently of childhood social inequalities in predicting all-cause mortality. There may of course be alternative early-life factors contributing to confounding that were not covariates of the cohorts reviewed here. Among three studies that adjusted for birth weight in multivariate-adjusted models, one reported no change from unadjusted models (Leon et al., 2009), and two reported a risk attenuation of 1% and 4%, respectively, compared with models that adjusted for childhood SES (Osler et al., 2003) and education (Jokela, Batty, et al., 2009). However, recent evidence suggests that birth weight may not be the ideal indicator for exposures in the intrauterine environment, which carry their most critical influence on neurological and physiological development during the early prenatal period (Kelly, 2009). Other qualitative characteristics in early childhood may further

explain the relationship between premorbid intelligence and longevity (Kilgour et al., 2009) including style of parenting and cognitive stimulation at home (Guo & Harris, 2000), or the effects of diet. However, so far, the potential confounding of these early-life factors have not been demonstrated, and these other suggested variables are likely to be associated with parental intelligence.

Attenuation of the intelligence–mortality association

Education and adult SES were found partially to attenuate the risk of mortality according to a one *SD* advantage in intelligence. Premorbid cognitive ability may act via occupational status and wealth to reduce the risk of mortality, by providing a less hazardous work environment, a safer and more comfortable home environment, and the material means to access better and more immediate medical care. Furthermore, intelligence may be mediated by education to reduce the likelihood of death, perhaps by increasing a person's receptivity to health education messages (thereby reducing negative behaviours such as smoking and excess alcohol consumption, and promoting exercise and healthy eating), and by improving comprehension of medical terminology and instruction that impacts on disease management and prevention. Nevertheless, the results to date cannot tell us for certain whether education and adult SES are simply partial mediators of the association between intelligence and mortality, or whether the results reflect overadjustments if both factors are partial surrogates for intelligence, or if these variables confound intelligence–mortality associations (Batty & Deary, 2005). Structural equation modelling can examine for statistical mediation, and one study to employ this technique reported that the effect of a general intelligence factor on mortality was entirely mediated by income, education and poor physical health in adulthood (Weiss et al., 2009). However, in this study, with cognitive ability measured at age 20 years, the association between intelligence and mortality could also have been partially confounded by education. In this chapter's meta-analysis, two out of five studies that adjusted for adult SES (Hemmingsson et al., 2006; Batty, Shipley, Mortensen, Boyle, et al., 2008), and three out of six studies adjusting for education (Batty, Wennerstad, et al., 2009; Jokela, Elovainio, et al., 2009; Batty,

Shipley, & Mortensen, et al., 2008) had intelligence test scores measured in later youth (19 to 20 years of age), when most people have completed education. There is evidence for a causal association from childhood intelligence scores to later educational achievement in longitudinal studies, and it is also likely educational experience can boost cognitive test scores to some extent (Deary & Johnson, 2010). Therefore reciprocal dynamic pathways between intelligence, education and adult SES need to be considered.

Few studies in the meta-analysis adjusted for both education and adult SES in the same model. It is suggested that both factors may overlap in their attenuation effects on the intelligence–mortality association (Link et al., 2008), but there is also evidence to show that they are not interchangeable, and have independent effects on health outcomes (Geyer et al., 2006; Martikainen, Blomgren, & Valkonen, 2007). Among three studies to control simultaneously for adult SES and education, the relative risk of mortality was entirely attenuated (Jokela, Batty, et al., 2009; Kuh et al., 2009; Jokela, Elovainio, et al., 2009). Interpretation of these findings should also consider the likelihood of overadjustment. In studies that reported complete attenuation effects of the intelligence–mortality gradient after multivariate adjustments, in addition to controlling for socioeconomic and educational variables, it was noted that three studies adjusted for smoking (Jokela, Batty, et al., 2009; Kuh et al., 2009; Batty, Shipley, Mortensen, Boyle, et al., 2008), two adjusted for alcohol consumption (Jokela, Batty, et al., 2009; Batty, Shipley, Mortensen, Boyle, et al., 2008) and there were further adjustments made for psychiatric illness (Batty, Shipley, Mortensen, Boyle, et al., 2008), parental interest in a child's education (Jokela, Batty, et al., 2009), or the quality and care of a household (Kuh et al., 2009). These potential explanatory factors are worthy of further investigation, particularly as two of these (smoking and alcohol consumption) are important risk factors for various chronic diseases.

Future directions

The present meta-analysis was unable to consider cause of death in the intelligence–mortality association, but this would seem an important area for future

systematic review, particularly as it was likely to have driven the stronger effect sizes of cohorts followed to younger ages in adulthood. For example, it may be that intelligence has a stronger relation to mortality caused by external events such as accidents (O'Toole et al., 1988), more prevalent among younger adults, than cause-specific mortalities more typical in later life (Hart et al., 2003). Studies have already replicated the inverse association between premorbid intelligence and cardiovascular disease-related mortality, with increased effect size magnitudes for coronary heart disease-related deaths compared with stroke-related deaths (Batty, Wennerstad, et al., 2009; Batty, Mortensen, Andersen, et al., 2005; Batty, Shipley, Mortsensen, Gale, & Deary, 2008; Hemmingsson, Essen, Melin, Allebeck, & Lundberg, 2007; Lawlor et al., 2008) (Batty, Mortensen, Andersen, et al., 2005). The relationship between childhood cognitive ability and risk of cancer mortality is also likely to vary by type (Hart et al., 2003). For example, smoking-related cancers might carry a stronger association with intelligence (Hart et al., 2003; Taylor et al., 2005) than other cancer types (Batty, Mortsensen, Gale, et al., 2009). Specific causes of death are therefore likely to be crucial in providing explanations as to why intelligence predicts life expectancy, and larger cohorts with increased numbers of cause-specific mortalities will help to clarify this issue.

In the present study it was found that education and social position in adulthood are factors that may help to account for the intelligence–all-cause mortality association. However, the extent to which these SES indicators act as partial surrogates for intelligence, or mediators and/or confounders of the intelligence–mortality association requires formal testing. Future longitudinal studies of mortality risk with repeated measures of intelligence, education, and adult SES, spanning childhood to adulthood could contribute to this. Twin studies to determine the extent to which intelligence shares genetic and environmental causes with health, education, and social class, in predicting mortality, will also help to inform this issue. With evidence of associations between cognitive performance and education showing substantial heritability (Bartels, Rietveld, Van Baal, & Boomsma, 2002; Johnson, McGue, & Iacono, 2006) it is possible that these variables may share some genetic effects in predicting death. Although early-life SES did not help to explain the intelligence–mortality association and birth weight is another unlikely

confounder, future studies could explore alternative early-life variables, in particular the intrauterine environment, and how these might simultaneously determine neurological and physiological integrity, in interaction with genetic influences, leading to lifelong effects on cognition and health.

Table 2.1 Characteristics of 27 longitudinal cohort studies of premorbid intelligence and all-cause mortality.

Study	Country, study name	Sex	Birth yr	Age at IQ test, yr (*M*)	Mortality period (follow-up in yr) [a]	Cohort *N*	Deaths, n	IQ test, cohort type	Model adjustments
*O'Toole et al. (1988) [b]	Australia, Veterans Health Studies	M	1947-53 (includes earlier periods)	≥18	1967-1982 (2 to 17)	2,309	523	AGCT, conscription	Basic model: Unspecified Multiple adjustments: Post-school course, no of jobs; and during 2-year service history: AWOL offence, alcohol offence, duration of hospital stay, motor vehicle charge
*Whalley and Deary (2001)	UK, SMS32 Aberdeen Cohort	M & F	1921	11	1932-1997 (1 to 65)	M 1,153 W 1,032	M 646 W 438	Moray House No. 12, school	Basic model: Age
Deary et al. (2003)	UK, SMS32 Aberdeen Cohort	M & F	1921	11	1932-1997 (1 to 65)	M 1,139 W 1,032	M 633 W 438	Moray House No. 12, school	—
*Hart et al. (2003)	UK, SMS32 and Mid-span studies	M & F	1921	11	1970-2001 (38 to 69)	922	422	Moray House, school	Basic model: Sex and age Adult SES: Basic model + adult social class Multiple adjustments: Adult SES model + deprivation
*Osler et al. (2003)	Denmark, Metropolit2000	M	1953	12	1968-1998 (3 to 33)	7,308	522	Harnquist, school	Basic model: Unspecified Childhood SES: Father's social class Multiple adjustments: Childhood SES model + birth weight
Deary et al. (2004)	UK, SMS47 Six Day Sample	M & F	1936	11	1968-2000 (21 to 53)	908	125	Binet test, school	—

Kuh et al. (2004)	UK, National Survey of Health and Development (British 1946 birth cohort)	M & F	1946	8	1971-2000 (17 to 46)	M 2,192 W 2,057	M 133 W 96	NFER tests, school	—
Hart et al. (2005)	UK, SMS32 and Mid-span studies	M & F	1921	11	1970-2001 (38 to 69)	938	432	Moray House, school	—
*Martin and Kubzansky (2005)	USA, Terman Life Cycle Study	M & F	1903-16	6-18 (11)	1922-1986 (1 to 64)	862	293	Stanford-Binet, school	Basic model: Sex Childhood SES: Poor health and father's occupation
*Hemmingsson et al. (2006)	Sweden, Army Conscripts	M	1949-51	18-20 (19)	1971-2000 (1-31)	49,262	2,022	SEB 1967, conscription	Basic model: Unadjusted Childhood SES: Father's occupation at age 9-11 Adult SES: Adulthood socioeconomic position Multiple adjustments: All above models
Vagero et al. (2006)	Sweden, Army Conscripts (Stockholm Birth Cohort Study)	M	1953	(18)	1980-2002 (9 to 31)	6,318	204	SEB, conscription	—
*Pearce et al. (2006)	UK, Newcastle Thousand Families	M & F	1947	11	1959-2003 (1 to 45)	M 357 W 360	M 30 W 19	Moray House Nos. 57 & 58, school	Basic model: Unspecified Childhood SES: Father's social class at birth (mother's if unavailable)
*Holsinger et al. (2007) [c]	USA, NAC-NRC Twin WWII Veterans	M	1917-27	17-21 (19)	1967-2004 (22 to 59)	984	385	AGCT / GCT, conscription	Basic model: Unspecified
Batty, Gale et al. (2008)	USA, Vietnam Experience Study	M	1947	(19)	1985-2000 (18 to 33)	4,157	231	Army General Technical, conscription	—

*Batty, Shipley, Mortensen, Boyle, et al. (2008) [d]	USA, Vietnam Experience Study	M	1947	(20)	1985-2000 (18 to 33)	4,316	241	Army General Technical, conscription	Basic model: Age Education: Educational level attained Adult SES: Occupational prestige, educational grade & family income Multiple adjustments: Basic model + adult SES model + rank, ethnicity, depression, BMI, pulse rate, posttraumatic stress disorder, somatic disease, martial status, alcohol consumption, blood pressure, blood glucose, generalised anxiety disorder, smoking, FEV1
*Deary et al. (2008)	UK, SMS47 Six Day Sample	M & F	1936	11	1968-2003 (21 to 56)	1,181	193	Binet test, school	Basic model: With and without sex (no difference) Education: Years of education Adult SES: Occupational social class Multiple adjustments: Sex and dependability
Starr et al. (2008)	UK, SMS32 Aberdeen Cohort	M & F	1921	11	1932-2007 (1 to 75)	M 202 W 152	M 102 W 56	Moray House No. 12, school	—
Batty, Mortensen et al. (2008)	USA, Vietnam Experience Study	M	1947	(20)	1985-2000 (18 to 33)	14,437	769	Army General Technical, conscription	—
Batty, Shipley, Gale et al. (2008)	USA, Vietnam Experience Study	M	1947	(20)	1985-2000 (18 to 33)	4,166	233	Army General Technical, conscription	—
*Batty, Wennerstad, et al. (2009)	Sweden, Army Conscripts	M	1950-76	16-26 (18)	1971-2001 (1 to 30)	994,262	14,498	SEB, conscription	Basic model: Age, year of birth, conscription testing centre Childhood SES: Parental socioeconomic index (highest of either parent), height Education: Educational level attained + multiple adjustments (see below) Multiple adjustments: Basic model + childhood SES model + body mass index, blood pressure, psychiatric and somatic illness

*Jokela, Elovainio et al. (2009)	USA, National Longitudinal Study of Youth	M & F	1957-64	16-23 (19)	1980-2004 (0 to 24)	M 5,682 W 5,639	M 248 W 112	AFQT, research sample	Basic model: Sex, birth year, ethnicity, health status Education: Basic model + years of education and marital status Multiple adjustments: Education model + household income
*Kuh et al. (2009)	UK, National Survey of Health and Development (British 1946 birth cohort)	M & F	1946	8, 11, 15	1971-2005 (10 to 51)	4,128	M 195 W 137	NFER tests, school	Basic model: Sex Multiple adjustments: Basic model + father's social class, mother's & father's education, care of house & child, adult housing quality & tenure, adult social class, household income, smoking, education.
Weiss et al. (2009)	USA, Vietnam Experience Study	M	1947	(20)	1985-2000 (18 to 33)	4,200	234	Army General Technical, conscription	—
Hemmingsson et al. (2009)	Sweden, Army Conscripts	M	1949-51	18-20 (19)	1990-2003 (19 to 36)	43,834	Not reported	SEB 1967, conscription	—
*Jokela, Batty et al. (2009) [e]	UK, National Child Development Survey (British 1958 birth cohort)	M & F	1958	11	1969-2004 (1 to 35)	14,132	M 213 W 116	NFER tests, school	Basic model: Unspecified Childhood SES: Father's occupational class Adult SES: Occupational class Education: Educational level attained Multiple adjustments: All previous models + child covariates (family difficulties, family size, problem behaviour, birth weight, height, mother's interest in child education, father's interest in child education), and adult covariates (marital status, psychosomatic symptoms, smoking, alcohol consumption, body mass index)
*Leon et al. (2009)	UK, ACONF	M & F	1955	7	1970-2007 (8 to 45)	11,603	M 426 W 235	Moray House Picture Tests Nos. 1 & 2, school	Basic model: Age, sex Childhood SES: Perinatal factors (which didn't alter the basic model), father's social class at birth, family size Multiple adjustments: All previous models + childhood height and weight

*Lager et al. (2009)	Sweden, Malmö Longitudinal Study	M & F	1927-28	10	1939-2003 (1 to 65)	M 832 W 698	M 363 W 176	Hallgren test, school	Basic model: Unadjusted Childhood SES: Father's education Education: Educational level attained

Note. Studies appear in publication date order; those marked with an asterisk are included in the meta-analysis. ACONF = Aberdeen Children of the 1950s; AFQT = Armed Forces Qualification Test; AGCT = Army General Classification Test; GCT = General Classification Test; NFER = National Foundation for Educational Research; SMS32 = Scottish Mental Surveys of 1932; SMS47 = Scottish Mental Surveys of 1947; SEB = Swedish Enlistment Battery; M = men; W = women.
[a] If years of follow-up and/or dates were not reported these were estimated according to the theoretically longest time period.
[b] Study included all deceased and a random sample of survivors from the original cohort, twice as large as the deceased group.
[c] Years since cognitive testing is an estimate: In correspondence Holsinger et al. reported that the vast majority of conscripts would have been 17 to 21-years-old at testing.
[d] Years since cognitive testing and birth-year are approximations based on the mean age of participants at the beginning of follow-up in 1985-86.
[e] Models for sex groups and those that adjusted for adult SES and multiple variables are based on a shorter follow-up period (23-46 years) and therefore a smaller sample size (*N* = 10,620).

Table 2.2 Sensitivity analysis: Summaries of all-cause mortality risk in relation to a one *SD* advantage in premorbid intelligence.

Subgroups	*N* studies	Reference # (see Appendix A)	*N* deaths	*HR* (95% CI)	Heterogeneity		Attenuation from basic model
					p	I^2 (%) [a]	
Basic model	16	All	22,453	0.76 (0.75-0.77)	0.28	15.5	
Age (*M*) at IQ							
7-12 yrs	10	3-4, 7, 9-12, 14-16	4,424	0.80 (0.77-0.83)	.61	0.0	
18-20 yrs	6	1-2, 5-6, 8, 13	18,029	0.75 (0.74-0.77)	.54	0.0	
% ascertainment							
< 80%	7	1-2, 4, 9, 14-16	17,148	0.76 (0.75-0.78)	.39	5.4	
≥ 80%	7	3, 5, 7-8, 10-12	4,397	0.77 (0.74-0.80)	.25	23.7	
Invalid [b]	2	6, 13	908	—	—	—	
Effect size							
HR	12	1-5, 9-12, 14-16	20,856	0.76 (0.75-0.78)	.24	21.1	
OR	4	6-8, 13	1,597	0.71 (0.64-0.79)	.57	0.0	
Cohort size							
< 1,000	4	4, 6, 12, 15	1,149	0.83 (0.76-0.91)	.26	25.3	
1,000 – 10,000	7	1, 3, 9-10, 13-14, 16	3,638	0.77 (0.74-0.81)	.30	17.4	
> 10,000	5	2, 5, 7-8	17,870	0.76 (0.74-0.77)	.70	0.0	
Follow-up duration							
< 40 years	7	1-2, 5, 7-8, 13-14	18,495	0.75 (0.74-0.77)	.71	0.0	
40-69 years	9	3-4, 6, 9-12, 15-16 11	3,958	0.80 (0.77-0.83)	.50	0.0	
Cohort birth year							
1910s-20s	5	4, 6, 10, 12, 16	2,723	0.82 (0.77-0.86)	.41	0.0	
1930s-40s	4	1, 3, 9, 15	815	0.73 (0.65-0.80)	.80	0.0	
1950s-60s	7	2, 5, 7-8, 11, 13-14	14,858	0.76 (0.74-0.77)	.56	0.0	
Sex [c]							
Female	7	7-11, 15-16	1,086	0.78 (0.73-0.84)	.17	33.4	
Male	7	as above	1,771	0.80 (0.76-0.85)	.88	0.0	
Adjusted for:							
Child SES	9	2-3, 5, 7, 10-12, 14-15	18,733	0.77 (0.75-0.79)	.48	0.0	[d] 4.0%
Adult SES	5	1, 3-5, 7	3,070	0.84 (0.78-0.90)	.52	0.0	33.5%
Education	6	1-3, 7-8, 10	16,023	0.89 (0.86-0.91)	.53	0.0	[d] 54.2%

Note. All hazard ratios are estimated from fixed effects models.
[a] Percentage of variation across studies due to heterogeneity.
[b] Insufficient data prevented estimation of ascertainment rate at follow-up.
[c] Number of deaths reported for men and women exclude data from Jokela, Elovainio, et al. (2009) which was unreported.
[d] Removing by far the largest cohort (Batty, Wennerstad, et al. 2009) gave attenuation effects by childhood SES of 0.0% and by education of 45.8%.

Figure 2.1 Flow diagram of articles selected for systematic review and meta-analysis.

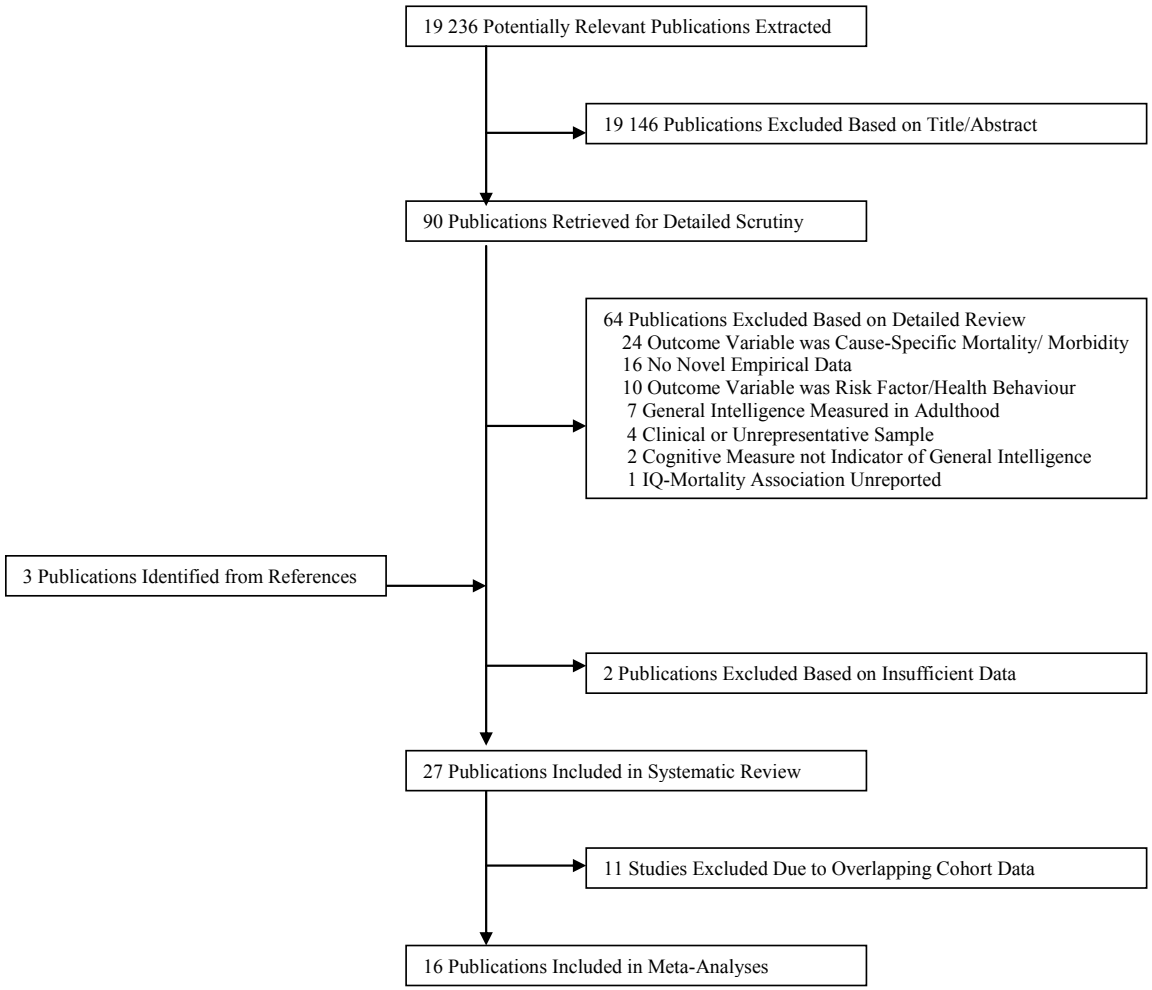
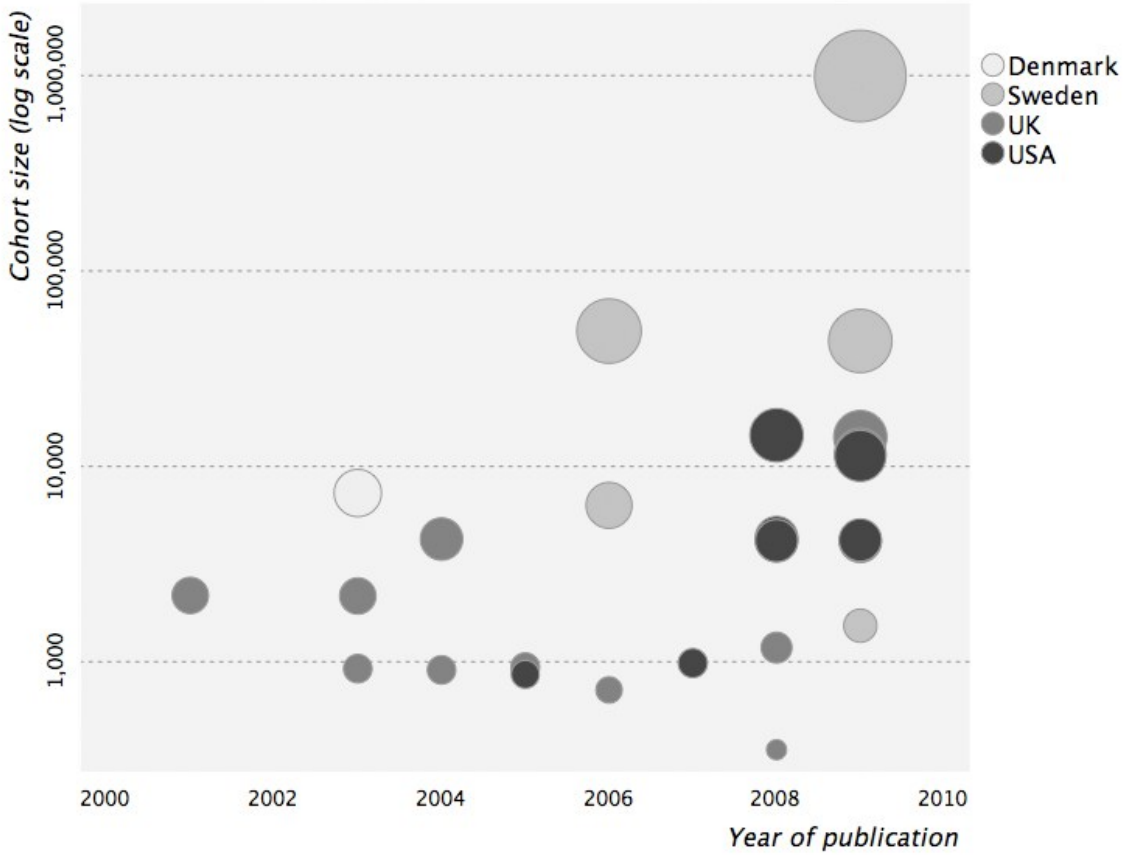
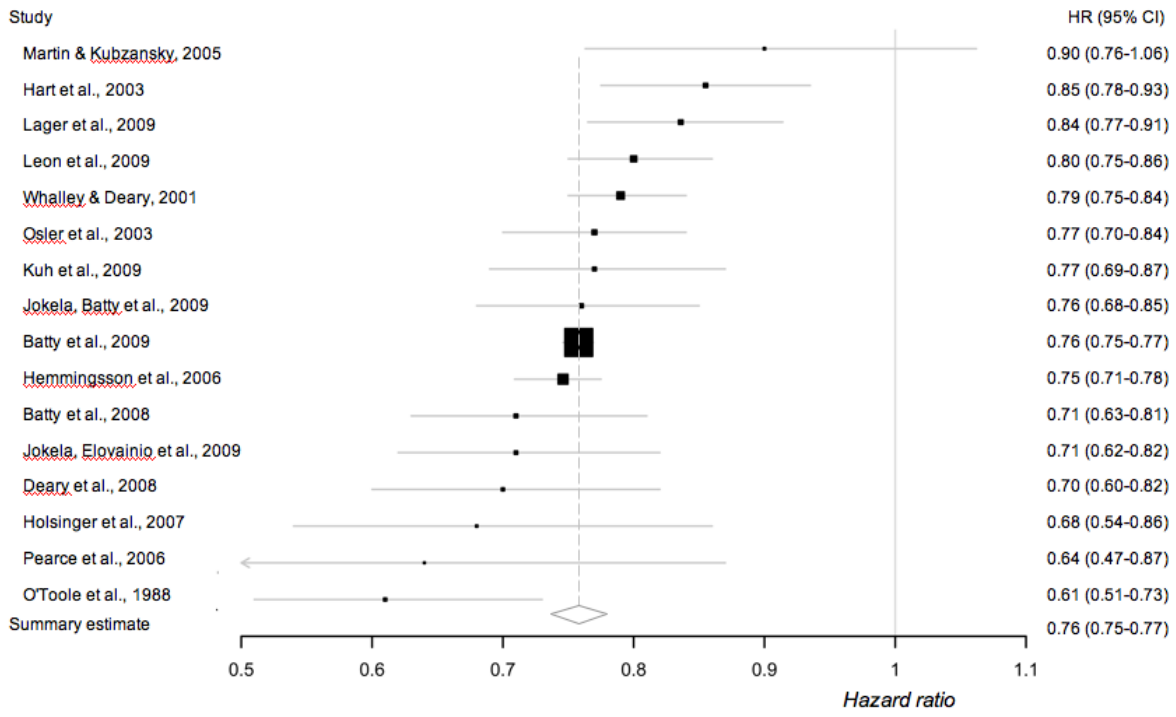


Figure 2.2 Publication rate of longitudinal cohort studies on premorbid intelligence and all-cause mortality, *N* = 27.



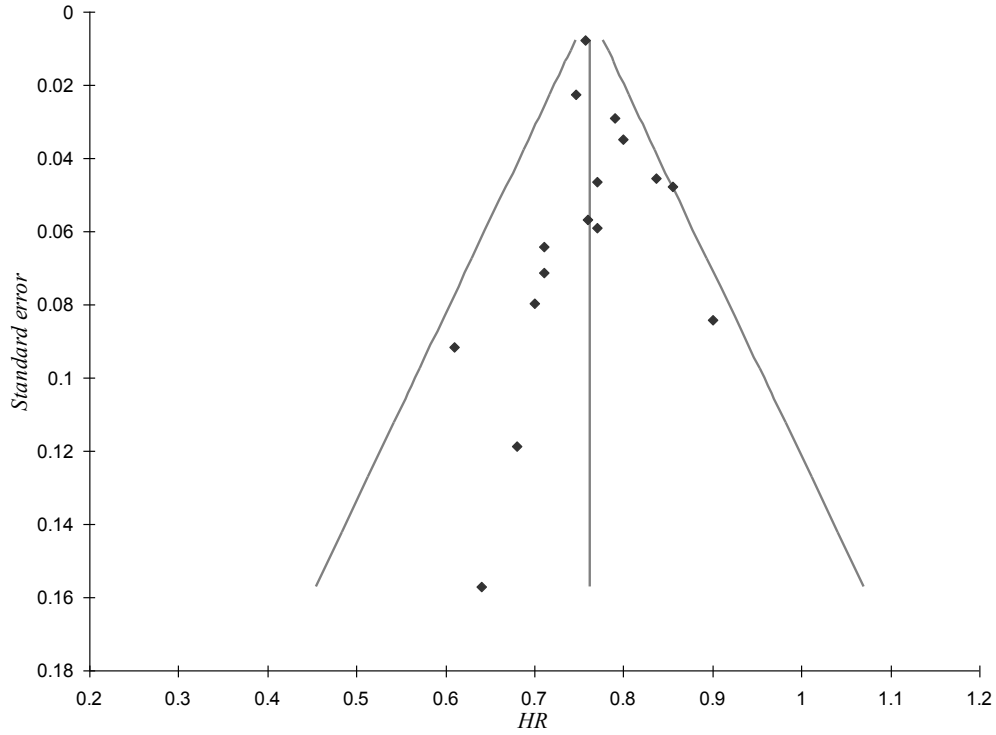
Note. Circles are shaded to represent country of origin and scaled proportionately to cohort size. One study is missing (O'Toole et al., 1988) as its publication precedes 2000.

Figure 2.3 Risk of total mortality per one *SD* advantage in intelligence test scores, *N* = 16.



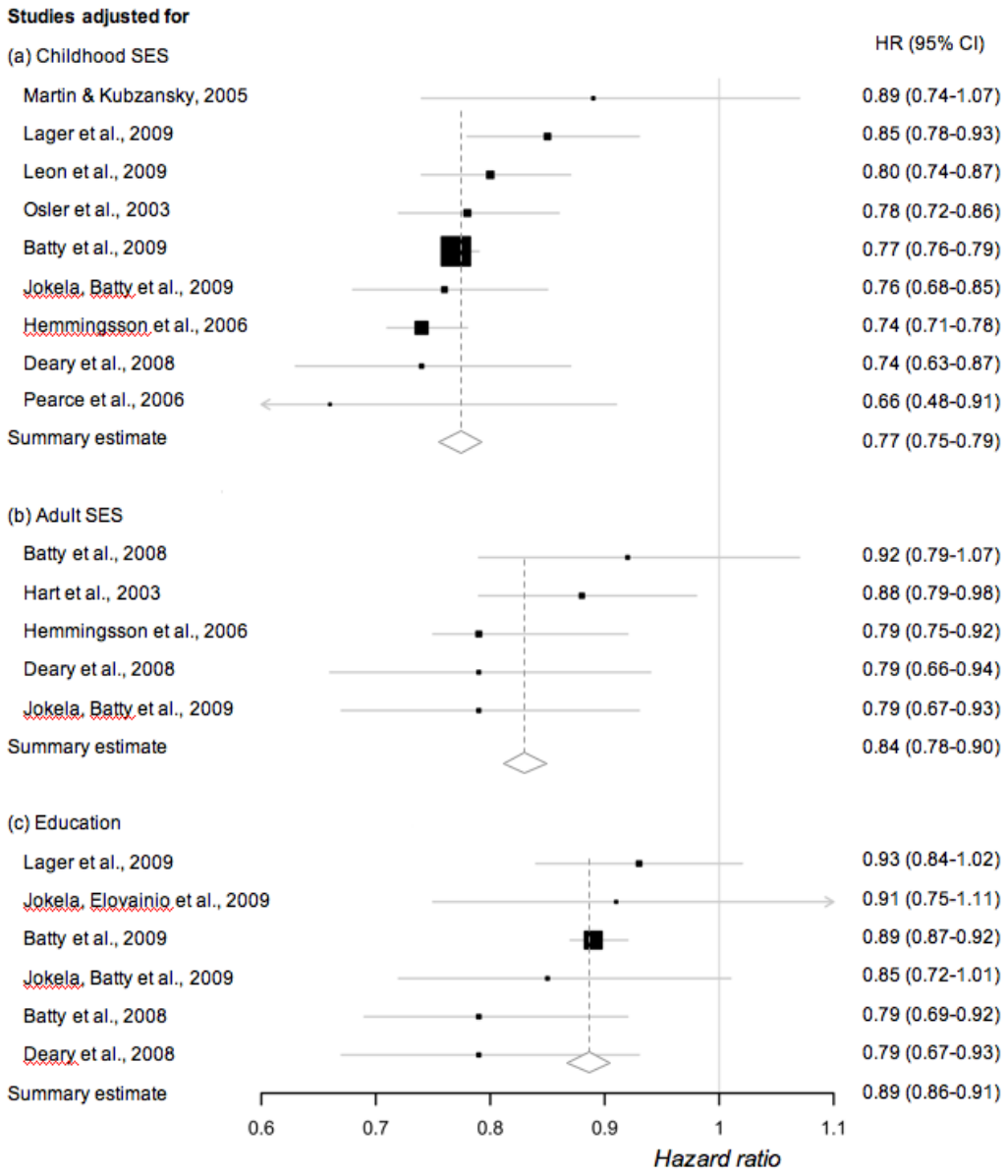
Note. Squares mark cohort-specific effect sizes, which are proportional to the statistical weight (*i.e.* inverse variance), and diamond indicates the aggregate effect size. Horizontal lines represent 95% CI.

Figure 2.4 Funnel plot of hazard ratios and standard errors demonstrating low publication bias.



Note. Diagonal lines indicate 95% CI of the aggregate hazard ratio (shown by vertical line) from all studies combined. One study (Hart et al., 2003) is an outlier of the CI parameters.

Figure 2.5 Risk of total mortality per one *SD* advantage in intelligence test scores after adjustment for: (a) Childhood SES, (b) Adult SES and (c) Education.



Note. Squares mark cohort-specific effect sizes, which are proportional to the statistical weight (i.e. inverse variance), and diamonds indicate the aggregate effect sizes for studies adjusted for each covariate. Horizontal lines represent 95% CI.

Chapter 3
Genetic covariance of intelligence and academic achievement in a UK-population cohort

The role of educational inequality in understanding the link between intelligence differences and mortality risk cannot be underestimated; most studies in cognitive epidemiology control for its effects (if data on years in education or academic attainment exist). In the previous chapter it was observed that controlling for educational variables reduced the IQ-mortality effect size by half. This is one of the strongest attenuation effects reported in cognitive epidemiology, which could be a mediation effect, confounding, or both. However, as discussed, education may also act as a partial surrogate for cognitive abilities in such models, thus attenuation effects are overadjusted. This latter possibility may be validated by behaviour genetic twin studies, which report substantial heritability of the association between cognitive performance and education variables (Bartels et al., 2002; Johnson et al., 2006). However, these studies have relied upon preselected pairs of twins that may not be a fully representative sample of the background population. Selection bias may be generous to additive genetic effect estimates. This chapter and the next, present behaviour genetics studies from two whole population samples of schoolchildren, including random samples of twins and singletons, to estimate the heritability of education-intelligence associations. The present chapter presents data from 2004, from the UK.

Intelligence and education: A strong phenotypic association

Intelligence test scores, and academic achievement measured at the same age or older, correlate strongly ($r > .60$) in national samples of schoolchildren (Bartels et al., 2002; Deary et al., 2007). The underlying causes of this association however are a subject of current debate. This is for several reasons. First, understanding the distinction between constructs of intelligence and academic achievement is of theoretical importance (Luo, Thompson, & Detterman, 2003). Second, if intelligence is directly causal to educational outcomes, and/or vice versa, this influences how

their independent effects on health and social outcomes (Calvin, Deary, et al., 2011; Lleras-Muney, 2005; Strenze, 2007) are modelled and interpreted in life course epidemiology (Deary & Johnson, 2010; Richards & Sacker, 2011). Third, the extent to which their association is genetically or environmentally determined has real-life implications for education and health policy (Petrill & Wilkerson, 2000). In the past few decades, family-based research largely on twins (Bartels et al., 2002; Petrill & Wilkerson, 2000; Kovas, Haworth, Dale, & Plomin, 2007; Thompson, Detterman, & Plomin, 1991; Wadsworth, DeFries, Fulker, & Plomin, 1995; Wainwright, Wright, Geffen, Luciano, & Martin, 2005), has provided evidence that a significant proportion of the phenotypic association between these two traits is due to genetic factors—as measured by genetic covariance. However, such studies may risk sampling and measurement bias, questioning the precision of their estimates. In the present study a whole population indirect twin design method is used to quantify additive genetic and environmental effects on the intelligence-education association using a large contemporary UK cohort with non-self-selected sampling.

Univariate heritability of two traits

General intelligence is a highly stable and heritable trait (Deary et al., 2009). Across all studies, additive genetic effects account for, on average, about half of the variance in cognitive test scores (Devlin, Daniels, & Roeder, 1997; Deary et al., 2006). These estimates become higher when measurement bias is low (Plomin, DeFries, McClearn, & McGuffin, 2009), and with increasing age from childhood to adulthood. For example, in the largest twin study to date, involving 11,000 twin pairs from four countries, heritability accounted for 41% of cognitive test score variance among 9 year-olds, 55% among 12 year-olds, and 66% of the variance observed in 17 year-olds. Shared environmental factors accounted for 33%, 18% and 16% respectively (Haworth et al. 2010). These concurrent trends are also reported by longitudinal childhood studies (Bartels et al., 2002; Kovas et al., 2007), and are evident for both verbal and nonverbal intelligence (Hoekstra, Bartels, & Boomsma, 2007). In the present study, a Dutch cohort includes data from three age groups, allowing us to consider this shift in genetic influence on intelligence over time.

Academic achievement is a more recent subject for behaviour genetics among general populations, but it too shows a significant heritable component. In the first study of a representative sample, the variance due to additive genetic effects in age-standardised language and mathematics achievement scores of 6 to 12 year-olds was 40% (Kovas et al., 2007, using data from Thompson et al., 1991). Since then, consistently high estimates have been reported from twin cohorts, with genetic inheritance accounting for in the region of 50% to 70% variance in, either, educational years, achievement test scores, or attainment levels (Bartels et al., 2002; Kovas et al., 2007; Baker, Treloar, Reynolds, Heath, & Martin, 1996; Johnson et al., 2006).

Twin studies of genetic covariance

Given the high correlation between intelligence and educational performance in national cohorts, and the significant heritability on each trait, it was always likely that, at least some genetic factors driving academic achievement were shared by those influencing intelligence trait variance (Martin, 1975). To test this, multivariate models using twin studies have produced estimates of the proportion of the phenotypic correlation between two traits due to genetic factors and due to the shared and non-shared environment respectively. In such studies genetic covariance estimates have been high, explaining a majority of the phenotypic association. Among 190 Dutch twin pairs, bivariate models applied to educational test scores at age 12 and IQ scores at ages 5, 7, 10 and 12 years (Bartels et al., 2002) observed additive genetic covariance that increased with age (40%, 75% and 83% among 5, 7 and 9 year-olds respectively), but became weaker again at age 12 (41%), with shared environment mainly accounting for the remaining association. An Australian study of 17 year-old students, including 256 monozygotic (MZ) and 326 dizygotic (DZ) twin pairs, reported high additive genetic covariance between the Queensland Core Skills Test and verbal and performance IQ scores; 72% and 75% respectively (Wainwright et al., 2005). However, the educational measure in this study may have been more aligned to conventional intelligence tests of deductive and inductive reasoning than to tests of educational curricula. Finally, the Twins‘ Early Development Study

(TEDS) analysed associations between teacher-rated academic attainment (in English, mathematics and science) and intelligence test scores of nearly 5,000 MZ and DZ twin pairs born in England and Wales between 1994 and 1996, each assessed at ages 7, 9, and 10 years (Kovas et al., 2007). Phenotypic correlations between traits were moderate and relatively stable over time (r = .37 to .41), and additive genetic covariance accounted for between 63% and 90% of these associations, with shared environment explaining the remaining covariance. Furthermore, these heritable effects were stronger among the oldest (83% to 90%) relative to youngest children (63% to 73%).

Selection bias in twin studies

It has therefore already been shown that additive genetic factors account for the majority of the phenotypic association between childhood intelligence and educational measures (at least from about 7 years), and that the degree of genetic covariance may increase with age. However, particular issues of sampling and measurement bias may limit the generalisability of these study estimates to background populations including non-twins. First, ratios of MZ to DZ twins are higher among twin study volunteers, relative to the general population of twins, a factor which, if not adjusted for, may significantly influence genetic effect estimates, most likely in the direction of underestimation (Lykken, McGue, & Tellegen, 1987). Second, the average cognitive abilities of volunteers tend to be higher than in the general population, including in twin samples (cf. Kovas et al., 2007; Rietveld, van Baal, Dolan, & Boomsma, 2000; Thompson et al., 1991; Wainwright et al., 2005); attrition in longitudinal studies also leads to higher ability and socioeconomic groups. These factors can have the converse effect of inflating heritability estimates (Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). The TEDS cohort reported attrition rates at 9 and 10 years, and so it cannot be ruled out that the increased heritability estimates with age in this study are in part influenced by of this form of self-selection bias.

Different testing procedures for phenotypic measurement may also influence genetic covariance estimates. The TEDS study had available various methods to

measure intelligence at different ages, including a telephone interview at age 7 years, parent-administered tests at 9, and internet-based tests aged 10. In the other longitudinal study to report genetic covariance estimates, a different intelligence test at ages 5, 7, and 10 years was used (Revisie Amsterdamse Kinder Intelligentie Test) compared to the revised Wechsler Intelligence Scale for Children (WISC-R) at 12 years (Bartels et al., 2002). This may have contributed to the discordant result of an increase in genetic covariance from age 5 to 10 years, and then a lower estimate at age 12. Although statistical adjustment can be made for sampling bias effects or weak inter-method reliability, analysing genetic covariance among non-self-selected twins, and using consistent methods of intelligence testing for investigating differential age effects, can be a more direct and reliable approach (Luo et al., 2003).

The present study

This study uses a twin extraction method applied to a national dataset from England, to remove the issue of self-selection bias of twins. The method was used previously to estimate univariate heritability of intelligence (Benyamin, Wilson, Whalley, Visscher, & Deary, 2005) and validated to a high level of accuracy (Webbink, Roeleveld, & Visscher, 2006). As this procedure also identifies individuals who are non-twins ("singletons"), their data is included to account for trait variability in the general population—a method rarely employed in the twin design. In this cohort all assessments of intelligence and academic achievement were group-administered within schools; the intelligence test has been well validated, and academic attainment was measured according to the national curricula of the UK in 2004. These factors may help to minimise measurement bias in the present study.
Additional to the main investigation of estimating genetic covariance between intelligence and academic achievement scores among a large UK cohort, these novel data are used to explore genetic components of *specific* cognitive abilities in relation to different educational subject achievement.

Methods

UK cohort

The cohort has been characterised in a previous report (Calvin, Fernandes, Smith, Visscher, & Deary, 2009). It originates from a cross-sectional linkage of routinely collected academic performance data from the UK Government's Department for Children, Schools and Families, and cognitive ability test data from 2004, maintained by a national school test provider (*GL Assessment*). The participants were 178,599 11 year-old boys and girls (M = 11 years 2 months; SD = 3.5 months), from 1,531 state and specialist schools in England, representing 93% of local education authorities.

Academic and intelligence assessments

Intelligence performance was measured in September to October 2004 using the age-standardised Cognitive Abilities Test — Third Edition (CAT3) of *verbal reasoning* (VR), *nonverbal reasoning* (NVR) and *quantitative reasoning* (QR) abilities (Smith, Fernandes, & Strand, 2001). Using principal components analysis a single unrotated general intelligence factor (*g*) was extracted and retained for analysis. The subtest score loadings on *g* were as follows: QR = .87, NVR = .85, VR = .8l.

Academic achievement data were taken from performance levels on Key Stage 2 curriculum tests in *English*, *mathematics*, and *science*, routinely group-administered within schools, using pencil and paper tests, during May 2004. The whole battery lasted five and a half hours (Directgov, 2011). These tests were designed to ensure that government targets for educational standards are met in England and Wales. Each individual had a rating from 2 to 5 recorded for each subject, reflecting raw scores in the ranges <21, 21-26, 27-32, and >32 respectively. These ratings were used as educational achievement scores in the analysis. A single educational factor score (*e*) was extracted from principal components analysis, accounting for 75% of the total score variance. This score was retained for analysis.

The subject score loadings on this general educational factor were as follows: English = .86, mathematics = .89, science = .89.

Twin identification

In this UK dataset twin status was allocated if two individuals matched on surname, date of birth, and school ID. Eighty eight individuals were removed because they were identified as triplets or quadruplets (for example, when more then two individuals matched on all three criteria), and the rest were assigned singleton status. Twins constituted 1.8% of the present study's cohort of singletons and twins from England—a somewhat smaller proportion than the 2.5% of individuals born as twins among total numbers of twins and singletons born in England and Wales in 1993 (Dunn & Macfarlane, 1996), which may be due for example to members of a twin pair attending different schools or a cotwin being absent on the day of testing.

Statistical Analyses

Data handling

The intelligence and education data were screened for missing data and normality, and assessed for univariate and bivariate outliers. If a member of a twin pair was excluded due to missing or outlier scores, their cotwin was also removed. As the educational data showed negative skew, scores of 2 were recoded as 3. Univariate outliers were values beyond three *SD*s from the mean, and bivariate outliers were detected if Mahalanobis distance was equal or higher of the critical value, 13.82 ($df = 2$, $p < .001$). The reduced sample sizes appear in Tables 3.1 and 3.2.

Modelling

Descriptive statistics and phenotypic correlations were produced using *PASW Statistics 17.0.3*. Phenotypic correlation coefficients were first calculated for the total

cohort, and then repeated, with the exclusion of one member from every designated twin pair, so that each data point was entirely independent.

ASReml Release 3.0 software (Gilmour, Gogel, Cullis, & Thompson, 2009) was used to estimate variance components and genetic and environmental effects in univariate and multivariate linear mixed models with the restricted maximum likelihood method (Visscher, Benyamin, & White, 2004). Without known zygosity in the present study's data, variance components for opposite-sex (OS) and same-sex (SS) twin pairs were derived instead of those for DZ and MZ twin pairs (see Benyamin et al., 2005; Scarr-Salapatek, 1971; Visscher et al., 2004). This method uses the knowledge that all OS twins are DZ and depends on the assumption that twice the proportion of OS twins is the proportion of DZ in the population[1]. Essentially the estimated proportions of covariance between twin pairs, attributed to additive genetic (A), shared environment (C), and unique environment (E) effects (Neale & Cardon, 1992), are weighted by the estimated proportion of MZ twins among SS pairs (p_{MZSS}), calculated with the formula[2]:

$$p_{MZSS} = (1 - 2p_{OS})/(1 - p_{OS})$$

where p_{OS} is the proportion of OS twins among total twin pairs

In the present study's UK cohort this parameter estimate was 0.53, based upon estimates of the proportion of MZ twins among total twin pairs of 36.2% in England, which can be compared to national statistics of 35.8%, reported by Imaizumi (2003).

In linear models *sex* and *age* were entered as fixed effect variables, to take out variation due to systematic effects. Given the inclusion of singleton data in the present study (unusual for a standard ACE twin design), the variables *pair* and *SS pair* were entered as random (latent) effects. The variable *pair* was a unique identifier assigned to each individual in the data unless it was shared by a member of

[1] This assumption is based upon the further assumption of a 1:1 sex ratio and equal survival, stemming from Weinberg's differential rule (Weinberg, 1901)
[2] Scarr-Salapatek (1971)

a twin pair. The variable *SS pair* was also a unique identifier given to each individual unless shared by a member of a SS twin pair:

$$y = \mu + \text{pair} + \text{SS pair} + \text{residual}$$
$$\text{With } \text{var}(y) = \text{var}(\text{pair}) + \text{var}(\text{SS pair}) + \text{var}(\text{residual})$$

In terms of covariances between twin pairs this implies:

$$\text{cov}(\text{SS pair}) = \text{var}(\text{pair}) + \text{var}(\text{SS pair})$$
$$\text{cov}(\text{OS pair}) = \text{var}(\text{pair})$$

The estimated variance components are therefore linear functions of the covariances of the SS and OS twin pairs, and their expectations are:

$$E[\text{var}(\text{SS pair})] = \text{cov}(\text{SS pair}) - \text{cov}(\text{OS pair})$$
$$E[\text{var}(\text{pair})] = \text{cov}(\text{OS pair})$$

Models of the underlying variance components in the population (e.g., A, C and E) are linear combinations of the covariances of SS and OS pairs, and therefore linear combinations of the estimated variance components.

In post-analytic procedures, variance components from REML were transformed and weighted using p_{MZSS} to estimate variation due to additive genetic (h^2), shared environment (c^2) and unique environment (e^2) effects among individual traits. These estimated parameters and the transformed and weighted cross-trait variance components were then used to estimate genetic covariance between traits (*Biv* h^2)—the proportion of their phenotypic correlation due to additive genetic factors (or the ratio of genetic to phenotypic covariance)—as well as covariance due to shared environment (*Biv* c^2) and unique environment (*Biv* e^2) effects. Sampling variances were calculated from a first order Taylor series of the likelihood function about the maximum likelihood estimates. Appendix C presents the formulae used in the post-analytic procedures.

Results

Comparison of singletons, opposite-sex twins and same-sex twins

Negligible differences were observed in the means and standard deviations of singletons, opposite-sex (OS) twins and same-sex (OS) twins on all cognitive and educational variables, in the British dataset (see Table 3.1), consistent with a previous report comparing singletons and total twin pairs in this cohort (Calvin et al., 2009).

Univariate models

Table 3.1 includes the intra-class correlations for OS and SS twin pairs; that these were higher for SS pairs, which would include all MZ twins and some DZ twins from the total sample, compared to OS twins who were all DZ, indicates additive genetic influences on all academic and intelligence variables. This was confirmed by the univariate estimates of additive genetic and environmental effects (see Figure 3.1). In the UK *g* was strongly heritable at age 11 (h^2 = .70 ±.14—which herein denotes the estimate and the standard error). Verbal and nonverbal reasoning scores showed higher heritability estimates (h^2 = .79 ±.14, and .70 ±.16, respectively) than quantitative reasoning scores (h^2 = .50 ±.15). Academic achievement in England's 11 year-olds was strongly influenced by additive genes, and the heritability estimate for the education factor score (h^2 = .75 ±.14) was equivalent to that of the intelligence factor, *g*. Among specific academic subjects, English was most strongly influenced by additive genetic effects (h^2 = .81 ±.16), followed by mathematics (h^2 = .66 ±.16) and science (h^2 = .51 ±16).

Multivariate models

Phenotypic correlations among all cognitive and academic variables were all positive and statistically significant ($p < .05$), with effect sizes ranging between r = .52 to .84, see Table 3.2). High genetic correlations with low standard errors were observed between cognitive subtest scores and academic attainments (r_G = 0.58 to 0.97) (see Table 3.3). Correlations of shared environmental effects were markedly high for some cross-trait pairings, for example of verbal reasoning with mathematics and science (r_C = 0.86 ±.36 and 1.0 ±.29, respectively), and quantitative reasoning with these two subjects (r_C = 1.00 ±.32 and 1.00 ±.33). By contrast, shared environment correlations were low for nonverbal reasoning with mathematics and science achievements (r_C = 0.05 ±.90 and, 0.24 ±.59, respectively), although in these latter models the standard errors were high.

A substantial proportion of the intelligence-education phenotypic correlations in the cohort were due to additive genetic influence, indicated by high genetic covariances (*Biv* h^2) in the range 0.53 to 1.00, with standard errors of between 0.13 and 0.21 (see Figure 3.2). These were consistently high between verbal reasoning and academic achievements (genetic covariance, *Biv* h^2 = 0.77 to 1.00), as well as nonverbal reasoning and the achievement scores (*Biv* h^2 = 0.94 to 0.98). Where environmental effects influenced phenotypic associations between quantitative reasoning and academic achievement, shared environment was somewhat more important in explaining the relationship (shared environment covariance, *Biv* c^2 = 0.22 to 0.34), than was the unique environment (*Biv* e^2 = 0.08 to 0.14).

Discussion

The main aim of this study was to report on genetic and environmental influences on associations between intelligence test scores and academic achievement scores in a large UK-wide cohort of schoolchildren. Although this is a relatively well-researched hypothesis in the behaviour genetics literature, the sampling method is novel in this context, providing cross-trait estimates using data on non-self-selected twin pairs and including trait distributions of singletons, thus eliminating self-selection bias. This method gives confidence when generalising

estimates to the background population. The substantial cross-trait heritabilities in an England cohort are consistent with the two most comparable previous studies of similarly aged children (Bartels et al., 2002; Kovas et al., 2007) and a third study of older children (Wainwright et al., 2005), in which pre- and/or self-selection of twin pairs may have increased genetic estimates. A strong additive genetic influence on intelligence and academic achievement associations is indicative of a more fundamental cognitive trait that is genetically influenced, and which drives a substantial proportion of the association between the two rather than, for example, individual differences in educational opportunity causing variance in intelligence test performance. Some evidence suggests that processing speed might be a reliable indicator of this low-level antecedent trait (Luo et al., 2003; Luciano et al., 2001), although in one study this variable shared a lower genetic correlation with academic achievement relative to other cognitive ability tasks, including memory and spatial reasoning (Thompson et al., 1991). It was also found that shared environment explained most of the remaining variance in England; that is, for the association between *g* and academic subject achievements, replicating previous studies' results (Bartels et al., 2002; Kovas et al., 2007; Wainwright et al., 2005).

Among twin studies of the association between cognitive performance and academic achievement, fewer have looked beyond a general intelligence score to using more specific functional tests of cognition. In one study, performance on verbal, spatial and memory tasks showed consistently high genetic correlations with language and mathematics achievement scores, and a processing speed task showed a relatively lower genetic correlation with academic achievement (Thompson et al., 1991). In another, a higher genetic correlation between verbal IQ and achievement scores was reported, relative to a performance IQ measure, although additive genetic effects explained an equally high proportion of the phenotypic association in both cases (Wainwright et al., 2005). In the present study's UK cohort, very high genetic correlations were observed between verbal reasoning and English language achievement, and nonverbal reasoning with mathematics and science achievements, which were greater than for other combinations of cognitive and academic variables. However, consistent with Wainwright et al. (2005) the present study observed equivalent and consistently very high genetic covariances between all three subject-

specific achievement scores and nonverbal and verbal reasoning respectively. This may further validate the proposition that additive genetic influences on a general cognitive processing trait drive associations with educational achievements, and that the effect of schooling in explaining variance in psychometric *g*, at least in primary school education, is a weakened proposition (Luo et al., 2003).

Although it was possible to look at performance on three distinct academic subjects in relation to specific cognitive subtest scores, the data were restricted so that it was not possible to consider different measures within academic subjects, which may differentially affect genetic covariance estimates. For example, in a U.S. twin study of elementary schoolchildren mathematical fluency and problem solving but not computational mathematics shared genetic covariance with cognitive ability (Hart, Petrill, Thompson, & Plomin, 2009). Studies such as this one, in an expanding area of behaviour genetics research with increasing complexity of multivariate models, include related performance measures such as reading, thereby deriving more reliable heritability estimates for the associations between cognitive ability and specific academic abilities once these covariates are controlled for. With the population-level cohort data available in the present study however, specific educational performance measures, and reading, could not be explored.

There are several strengths of the present study design worth highlighting, which must be counterbalanced with the weaknesses of the specific approach taken by this whole population twin study design. However, as the next chapter's Dutch study uses the same methodology, and bears many similarities to the present study's UK study—including age of cohort and equivalent measurements of intelligence and academic achievements—these are left for the Discussion section of Chapter 4, along with a comparison of these two studies' results.

Table 3.1 Descriptive statistics, and intraclass correlations of OS and SS twin pairs: England.

	Mean (SD)[a]			Skew	Kurtosis	*t*	
	Singletons *n* = 170,996	OS twin members *n* = 990	SS twin members *n* = 2112	All	All	OS twin pairs	SS twin pairs
Cognitive ability							
VR	0.00 (0.99)	-0.06 (0.98)	0.00 (0.99)	-0.06	-0.06	0.51	0.72
NVR	0.00 (1.00)	-0.06 (0.97)	0.03 (0.99)	0.22	-0.40	0.43	0.61
QR	0.00 (0.99)	-0.04 (0.97)	0.01 (0.98)	0.14	-0.37	0.46	0.59
g	0.00 (1.00)	-0.06 (0.97)	0.01 (0.98)	-0.01	-0.44	0.53	0.71
Education							
English	0.00 (1.00)	-0.01 (1.00)	0.03 (1.01)	-0.11	-0.84	0.38	0.59
Math	0.00 (1.00)	-0.02 (1.00)	-0.01 (0.99)	-0.15	-1.14	0.43	0.60
Science	0.00 (1.00)	0.01 (0.97)	0.02 (0.98)	-0.49	-0.75	0.44	0.57
e	0.00 (1.00)	-0.01 (1.00)	0.01 (1.00)	-0.31	-0.83	0.49	0.69

Note. *e* = education factor, *g* = general intelligence factor, Math = mathematics, NVR = nonverbal reasoning, OS = opposite sex, QR = quantitative reasoning, SS = same sex, *t* = intraclass correlation, VR = verbal reasoning

[a] ANOVA resulted in no statistically significant differences between the groups on any performance measure ($p < .05$)

Table 3.2 Intelligence and education phenotypic correlations: England.

	VR	NVR	QR	*g*	English	Math	Science
VR	-						
NVR	.69	-					
QR	.71	.74	-				
g	.89	.90	.91	-			
English	.71	.52	.59	.68	-		
Math	.67	.68	.77	.79	.61	-	
Science	.69	.61	.61	.71	.61	.67	-
e	.80	.70	.76	.84	.85	.88	.88

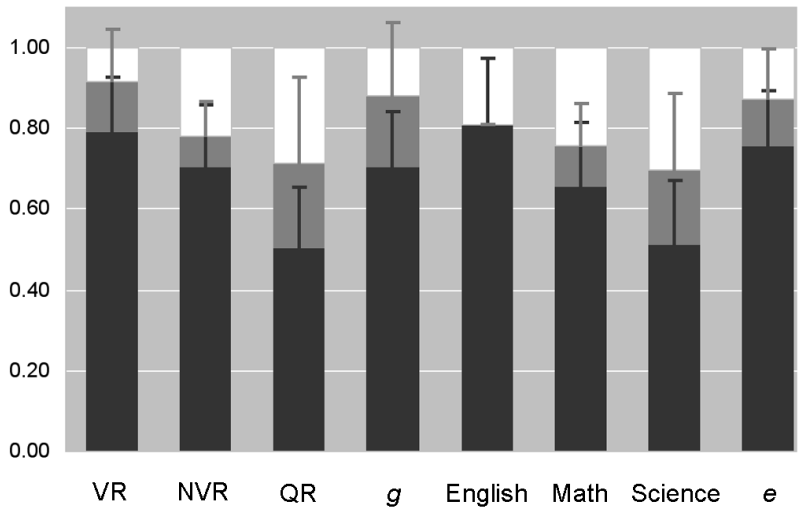
Note. Pearson correlation coefficients are reported for the total cohort (*N* = 174,098), and all are statistically significant at $p < .001$. *e* = education factor; *g* = general intelligence factor; NVR = nonverbal reasoning; QR = quantitative reasoning. Analyses were repeated following a random split of twin pairs to remove a cotwin from the dataset, and thus entirely independent data points; there were no changes to the coefficients.

Table 3.3 Bivariate genetic and shared environment correlations (and standard errors): England.

	English		Mathematics		Science		*e*	
	r_G	r_C	r_G	r_C	r_G	r_C	r_G	r_C
VR	0.92 (*0.06*)	- (-)	0.78 (*0.07*)	0.86 (*0.36*)	0.81 (*0.09*)	1.00 (*0.29*)	0.92 (*0.04*)	0.74 (*0.24*)
NVR	0.65 (*0.10*)	- (-)	0.96 (*0.08*)	0.05 (*0.90*)	0.97 (*0.12*)	0.24 (*0.59*)	0.92 (*0.07*)	0.19 (*0.70*)
QR	0.58 (*0.11*)	- (-)	0.85 (*0.08*)	1.00 (*0.32*)	0.62 (*0.14*)	1.00 (*0.33*)	0.75 (*0.08*)	1.00 (*0.34*)
g	0.79 (*0.07*)	- (-)	0.93 (*0.05*)	0.75 (*0.23*)	0.87 (*0.09*)	0.83 (*0.23*)	0.95 (*0.04*)	0.79 (*0.17*)

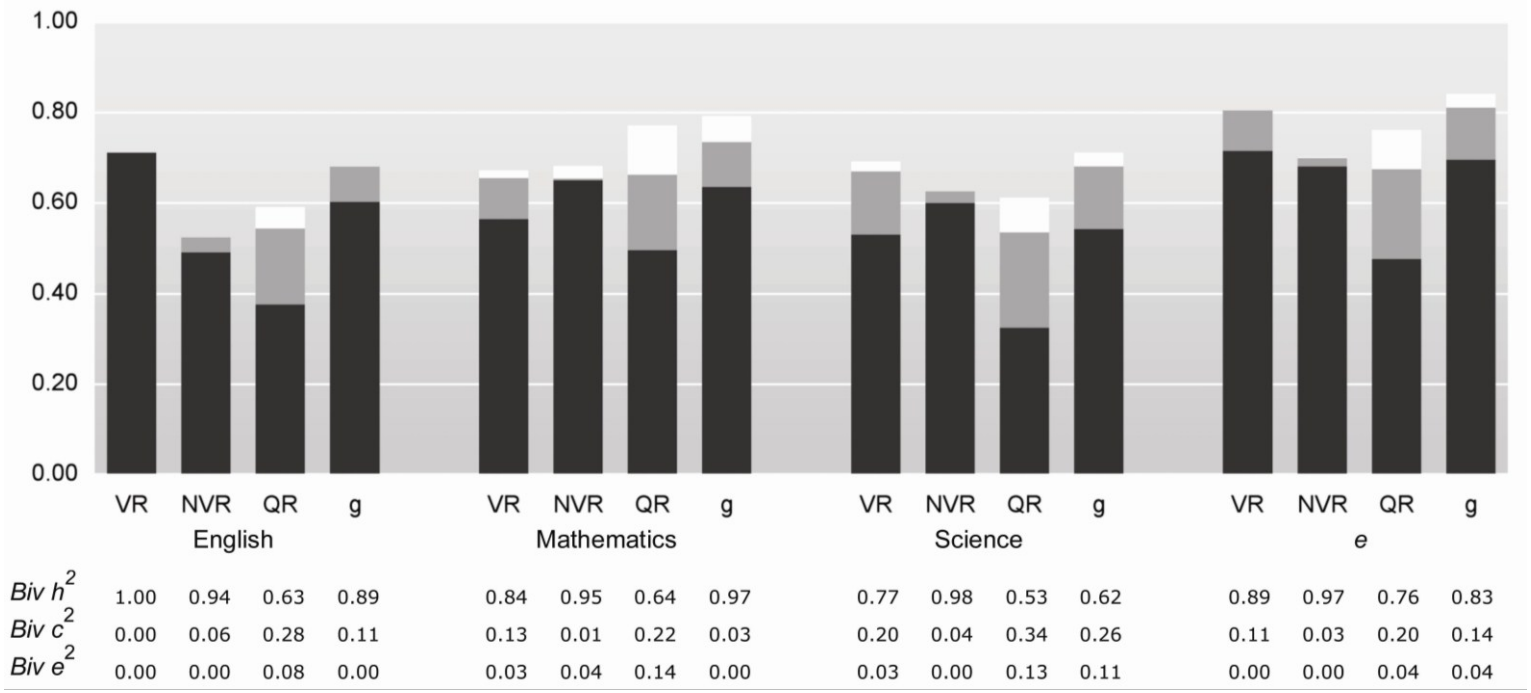
Note. Standard errors were not estimable for shared environmental correlations between English and intelligence test scores, due to a close-to-zero variance component and relatively large standard error in English. *e* = education factor; *g* = general intelligence factor; NVR = nonverbal reasoning; QR = quantitative reasoning; r_G = genetic correlation; r_C = shared environment correlation; VR = verbal reasoning.

Figure 3.1 Univariate estimates of additive genetic, shared and unique environment effects on intelligence and academic achievement: England.



Note. Bar shadings indicate the proportions of additive genetic (h^2; black), shared environment (c^2; grey), and unique environment (e^2; white) effects; error bars show the standard errors for h^2 and c^2. *e* = education factor; *g* = general intelligence factor; NVR = nonverbal reasoning; QR = quantitative reasoning; VR = verbal reasoning.

Figure 3.2 Covariance estimates of additive genetic, shared and unique environment effects: England.



	English				Mathematics				Science				*e*			
	VR	NVR	QR	g	VR	NVR	QR	g	VR	NVR	QR	g	VR	NVR	QR	g
Biv h^2	1.00	0.94	0.63	0.89	0.84	0.95	0.64	0.97	0.77	0.98	0.53	0.62	0.89	0.97	0.76	0.83
Biv c^2	0.00	0.06	0.28	0.11	0.13	0.01	0.22	0.03	0.20	0.04	0.34	0.26	0.11	0.03	0.20	0.14
Biv e^2	0.00	0.00	0.08	0.00	0.03	0.04	0.14	0.00	0.03	0.00	0.13	0.11	0.00	0.00	0.04	0.04

Note. Bars represent phenotypic correlations and their shadings indicate their relative proportions due to additive genetic (black), shared environment (grey), and unique environment (white) effects. Values beneath the bars correspond to the covariance estimates for additive genetic (*Biv* h^2), and shared (*Biv* c^2) and environmental effects (*Biv* e^2), which summed together equal 1.0. *e* = education factor; *g* = intelligence factor; NVR = nonverbal reasoning; QR = quantitative reasoning; VR = verbal reasoning.

Chapter 4
Genetic covariance of intelligence and academic achievement in The Netherlands

This chapter replicates the previous chapter in terms of hypothesis and design; that is, it uses the same twin extraction method and modelling techniques to estimate the proportion of phenotypic association between intelligence and academic achievement. However, in this study the cohort is derived from a population of Dutch schoolchildren. There are several factors that this cohort has in common with the previous study's British schoolchildren, enabling a valid cross-national comparison of intelligence-education genetic covariance estimates: The cohorts are of similar age; they share similar academic achievement tests, including language and arithmetic, which are measured according to the national curricula of the country; and, they are extremely large. The Dutch cohort also contains singleton data, and has not been preselected for twin pairs; rather it has derived from a population-representative study sample of Dutch schoolchildren. Furthermore, the present study's cohort is of an age when only core school subjects are studied as part of the curricula, and therefore, again the issue of controlling for variation in educational experience is minimised. A novel aspect of the present chapter however is the different ages of schoolchildren in The Netherlands, albeit consistent measures of intelligence and academic achievement are used across age groups. This allows for the opportunity to make comparisons of the effect sizes in three age groups, and a consideration in shift of genetic influence on intelligence and educational success over time. This may be relevant given evidence for increasing genetic covariance with age (Petrill & Wilkerson, 2000).

Methods

Dutch cohort

This cohort of schoolchildren from The Netherlands has been described in detail in a previous publication (Webbink, Posthuma, Boomsma, de Geus, & Visscher, 2008). It derives from the longitudinal PRIMA Survey, which aims to answer questions about educational strategies and performance in primary education in The Netherlands (Driessen, Van Langen, & Oudenhoven, 1994; Driessen, Van Langen, & Vierke, 2004). The present study incorporated data from the first five waves of the survey, which took place biannually from 1994 to 2002, and included ~60,000 pupils per wave. The PRIMA project targets a panel of ~600 schools at a time, stratified so that pupils from lower socioeconomic backgrounds are over-sampled. Measures of school performance and cognitive ability are administered to all pupils in grades 4, 6 and 8, corresponding to ages 8, 10 and 12 years. A minority of schoolchildren were included in more than one wave, so that in the present study, ~24% of those tested in grade 4 were also tested in grade 6 and, of these, ~7% were again tested in grade 8.

Academic and intelligence measures

The performance scores selected from this study are: *General intelligence* (IQ), as measured by two tests of nonverbal reasoning, specifically selected to minimise bias by socioeconomic status (Webbink et al., 2006), and, academic achievement scores in *arithmetic* (AR) and *language* (LA). Inter-method reliability among the same tests at different ages is reflected in high within-subject correlations among members of the cohort tested at more than one wave. Intraclass correlations are: IQ, .63 to 74, language, .62 to .76 and arithmetic, .70 to .83. Although in the present study, analyses are conducted separately for each age group, this evidence for reliability justifies a comparison of genetic estimates between the groups.

Twin identification

A similar method of twin identification was adopted in the Dutch data compared to the UK study (Webbink et al., 2006), with individuals matched on surname, date of birth, and school, and with ‘year of survey’ as a fourth matching

variable due to the multiple-wave design. In 1990 the proportion of individuals born as a twin among twin and singleton births in The Netherlands, was approximately 2.7% (Imaizumi, 2003). In the present cohort, twins constituted 2.0% of 8 year-olds, 1.8% of 10 year-olds, and 1.6% of 12 year-olds, again showing a somewhat lower representation compared to national statistics. It is comparable with the lower rate observed in the previous chapter's cohort.

Statistical Analyses

The statistical methods of the present study match those of the previous chapter, including the treatment of outliers, use of software, and the univariate and multivariate models. Zygosity was also unknown in this cohort, and so ACE models included a weighting, which was the estimated proportion of MZ twins among SS pairs:

$$p_{MZSS} = (1 - 2p_{OS})/(1 - p_{OS})$$

Where p_{OS} is the proportion of OS twins among total twin pairs.

The proportion of MZ twins among total twin pairs was estimated at 40.6% in the cohort, which is somewhat larger than the MZ twin birth rate in the Netherlands in 1990, recorded at 34.6% (Imaizumi, 2003). This resulted in an estimated weighting of 0.58 (averaged across age groups).

In linear models, as well as controlling for *sex* and *age*, *year of test* was included as a fixed effect to take out variation due to its systematic effects. As with the UK cohort, singleton data were also included in all models. For formulae to estimate variance components the Results section of Chapter 3 may be referred to. Appendix C includes formulae relating to post-analytic procedures.

Results

Comparison of singletons, opposite-sex twins, and same-sex twins

Negligible differences were observed in the means and standard deviations of singletons, opposite-sex (OS) twins and same-sex (SS) twins on all cognitive and educational variables, in the Dutch datasets (see Table 4.1), consistent with a previous report comparing singletons and total twin pairs (Webbink et al., 2008).

Univariate models

Table 4.1 includes the intra-class correlations on variable performance within OS and SS twin pairs; that these were higher for SS pairs, which would include all MZ twins and some DZ twins from the total sample, compared to OS twins who were all DZ, indicates additive genetic influences on all education and intelligence variables. This was confirmed by the univariate estimates of additive genetic and environmental effects (see Figure 4.1). The Dutch data support evidence that additive genetic effects on intelligence test performance increase with age, in the present study from 8 years (h^2 = .43 ±.23) to 12 years (h^2 = .67 ±.31). The data also show an unexpectedly low heritability estimate at age 10 years (h^2 =.24 ±.29), with a larger influence of shared environmental effects (c^2 =.29 ±.04) than might be expected given the existing literature.

In Dutch schoolchildren, language attainment showed greatest additive genetic influence in the younger cohort (h^2 = .74 ±.27) compared to ages 10 and 12 (h^2 = .43 ±.29 and .53 ±.31, respectively). Of the effect remaining, unique environmental influences were more important than shared environment. Arithmetic performance was largely heritable at 8 and 10 years (h^2 = .67 ±.27 and .73 ±.29 respectively), and unique environment explained the remaining variance. At age 12, additive genetic effects were relatively less important in explaining variance in arithmetic achievement (h^2 = .36 ±.27), and shared environment was more influential than at younger ages (c^2 = .35 ±.04).

Multivariate models

Phenotypic correlations among all cognitive and education variables, in the Dutch cohort, were all positive and statistically significant ($p < .05$). These effect sizes were smaller ($r = .36$ to $.47$) than compared with the England cohort, but the magnitude of associations was consistent across different ages. For example, at ages 8, 10 and 12, IQ-language correlations were $r = .38$, $.36$ and $.36$, and IQ-arithmetic correlations were $r = .44$, $.47$, and $.47$, respectively. On the other hand, correlations between the two educational subjects in The Netherlands showed an increase with older age groups, $r = .43$, $.50$ and $.55$, respectively. Intelligence was more strongly associated with arithmetic attainment compared to language attainment in both national cohorts.

Table 4.2 shows the genetic correlations between intelligence and education variables in The Netherlands. Genetic correlations between IQ and language, and IQ and arithmetic, were moderate across all ages ($r_G = 0.31$ to 0.58), with the exception of the cross-trait genetic correlation between IQ and language at age 8 ($r_G = 0.82$), which was higher, and more consistent with the UK data. An unexpected finding was that although shared environment correlations for IQ and educational attainment were negligible ($r_C = 0.00 \pm 0.00$) at 8 years and 12 years, among 10 year-olds they were high ($r_C = 0.74 \pm 0.56$ for language; 1.79 ± 3.02 for arithmetic), albeit with very high standard errors.

Figure 4.2 shows the genetic and environmental covariance estimates from the Dutch cohort. To consider the 8 and 12 year-old data first, these show that the language-IQ phenotypic associations were largely explained by additive genetic effects at both ages (*Biv* $h^2 = 1.00 \pm .43$ and $0.92 \pm .59$ respectively). Additive genes also explained the majority of the phenotypic association between arithmetic and IQ within these age groups (*Biv* $h^2 = 0.63 \pm .51$ at age 8 and $0.64 \pm .42$ at age 12), and the remainder was explained more by the shared than the unique environment (*Biv* $c^2 = 0.30$ and 0.20; *Biv* $e^2 = 0.07$ and 0.16 respectively). In contrast, at age 10, shared environment was more influential than additive genetic effects on the IQ and education phenotypic association (*Biv* $h^2 = 0.33 \pm .52$, *Biv* $c^2 = 0.49 \pm 0.38$ for language, and *Biv* $h^2 = 0.36 \pm .38$, *Biv* $c^2 = 0.45 \pm .28$ for arithmetic).

Discussion

The additive genetic covariance estimates between intelligence test performance and academic achievement scores from the present study's Dutch cohort, are at the high end of those reported from preselected twin study samples (Bartels et al., 2002; Kovas et al., 2007; Wainwright et al., 2005); at least, this is what was observed from the youngest and oldest age groups from the cohort. The remaining variance was explained mostly by effects of shared environment, which is again consistent with these previous studies. In a Dutch twin study of preselected twin pairs where zygosity was known, the genetic covariances (here meaning the proportion of the phenotypic correlation explained by additive genetic effects) between intelligence test scores at ages 7 and 10, and academic achievement at age 12, are similar in magnitude to those of the present study's 8 and 12 year-old cohorts where intelligence and academic achievement were measured contemporaneously (Bartels et al., 2002). However, the authors of this study, describing a sudden drop in genetic covariance between age 12-intelligence and academic achievement as "remarkable" (p. 550), interpreted it as shared environment influencing phenotypic associations in an age- and time-specific way. The present study observed a sudden drop in genetic covariance at age 10 rather than 12, although there were large standard errors around these parameter estimates.

Cohort effects

Comparison of estimates from two European countries

Lower genetic covariances, albeit with larger standard errors, were estimated in the Dutch relative to British cohort. There may be several explanations for this. One influence might be that the CAT-3 intelligence test used on the British cohort was designed to minimise demand on verbal skills (Smith et al., 2001), making it a less culturally biased intelligence indicator, and thus perhaps optimising the heritability estimates. An additional explanation for the relatively lower estimates in the Dutch cohort may be in its stratified sampling that increased representation of

low socioeconomic groups in the PRIMA Survey—particularly as lower heritability estimates for intelligence have been reported in these groups (Turkheimer et al., 2003). Nevertheless, there was notable consistency across the two cohorts' equivalent age groups; for example, in the additive genetic covariance estimates of intelligence with language and arithmetic/mathematics respectively, among 12 year-olds in The Netherlands and 11 year-olds in England. Another consistency was the greater additive genetic influence on intelligence-language associations, relative to intelligence-arithmetic associations, which is reported in the existing literature (Luo et al., 2003; Kovas et al., 2007).

Age effects on genetic covariance estimates

The different age groups of the Dutch schoolchildren provided the opportunity to consider changes in the magnitude of additive genetic influence on intelligence—education associations from age 8 to age 12, albeit using cross-sectional inference. Despite a general trend for genetic covariance to increase with age (Bartels et al., 2002; Kovas et al., 2007; Petrill & Wilkerson, 2000), one study reported a considerable decrease in the genetic covariance from 10 to 12 years (Bartels et al., 2002). The present chapter's findings showed no significant change in genetic covariance estimates between the youngest and oldest age groups however, and again, this may be because their standard errors were typically very large. It has been suggested that an initial increase in additive genetic influence at elementary school age may reflect emergent functionality of higher level cognition or a transition from rote learning to more complex academic engagement (Wainwright et al., 2005). Longitudinal twin studies running into secondary education would help to demarcate the ages at which additive genetic influences on intelligence-academic achievement associations shift in their relative importance.

Implications of the twin extraction method, and its strengths

Several key sources of potential bias were minimized in these last two chapters, including measurement bias (using well-standardised tests administered in

the stable classroom environment) and self-selection bias (random sampling from national cohorts). However, the twin extraction method could itself have incurred error, although a validation study reported a low risk of statistical bias using this method (Webbink et al., 2006). Error that did occur was due to false negative rather than false positive detection. Twins may have been under-detected in the present study (if for example, a cotwin was absent on the day of testing, had missing data, or attended a different school), particularly as a somewhat lower proportion of total twins were observed relative to national twin birth rates. This may compromise how twin population-representative the two cohorts might be. However, false negatives would have had to affect MZ twin pairs to a greater or lesser extent than DZ twins, in order to have influenced our effect sizes, and there is little to indicate that this might have been the case. Furthermore, estimates of the proportions of MZ twins among total twin pairs were similar to national birth statistics for the appropriate years (Imaizumi, 2003), albeit there was a slight overestimation of the MZ twin proportion in the Dutch cohort. A second potential source of error is the statistical approach, which is based on further assumptions than traditional approaches where zygosity is known. In particular, heritability estimates were derived from variance components of OS and SS twin pairs, weighted on the basis of statistical assumption. This was an estimation of the proportion of MZ twins among SS pairs, based upon the approximation that DZ twins represent two times the proportion of OS twins in the population, and assumptions of a 1:1 sex ratio among DZ twin births and an equivalent survival of male-male and female-female DZ twins. Furthermore, if there are sex-specific covariance estimates then the results risk bias.

Without known zygosity it is not possible to directly validate the twin extraction method within these cohort studies. An indirect method however is to look for consistency between univariate estimates of intelligence and education heritabilities reported here, with those from the existing literature, which was in fact found. In the present study, Dutch heritability estimates for intelligence were consistent with previous studies of similarly aged children (Bartels et al., 2002; Kovas et al., 2007; Haworth et al., 2010). The relatively low heritability of intelligence estimated in 10-year-old schoolchildren, and a greater influence of shared environment compared to other age groups, did show overlapping standard

errors of these estimates. In England, intelligence heritability was in the higher range of the existing literature, and this may be due to the measure's effective removal of cultural bias. However, different educational policies of The Netherlands and England may also influence disparities between these two countries' heritability estimates. For example, the relatively lower heritability of intelligence test performance in The Netherlands may be influenced by a greater effort by that country's government to create national equality in educational opportunities; Dutch schools receive additional personnel and resources for every additional pupil they teach who is from a disadvantaged background (Lindahl, Lindahl, Oosterbeck, & Webbink, 2007), which is likely to reduce genetic effects on the performance of tests taken in the school setting. On education, additive genetic effects on Dutch language were consistent with a previous estimate from the CITO test (Bartels et al., 2002), and heritability estimates of mathematics and science attainments in the British sample, were compatible with equivalent attainment scores in the UK TEDS study (Kovas et al., 2007). However, additive genetic effects accounted for 81% of the variance in English attainment compared to 60% in TEDS. The difference here may be that the present study's education data were based on a nationally standardised test score, compared to teacher ratings of scholastic achievement in the TEDS sample, which may have incurred within-classroom effects.

Study limitations

The methods employed in these two latest chapters overcame some key caveats of interpreting additive genetic effect estimates from ACE models (Neale, 2009), including use of large, non-preselected twin cohorts, and by incorporating singleton data in the models to account for trait variability in the general population. However, admittedly there are limitations of a standard twin design that the present studies share. First, the analytic method implicitly assumes that twin similarity due to common environmental effects is the same for MZ and DZ twins. A second assumption is that the genetic correlation between males and females is 1.0. Nevertheless, intelligence heritability estimates reported by twin studies depending on these first two assumptions, have recently been validated by the first genome-

wide association study using biological samples of unrelated adults, which found that genetic variation explained ~50% of individual differences in fluid intelligence (Davies et al., 2011). Third, and specific to an analysis of twins where zygosity is unknown, is the assumption that among DZ twins the effect of shared environment is the same for SS and OS twin pairs. In future, biological samples collected from national twin registries will enable a more thorough investigation of familial factors in the covariance between intelligence and academic achievements (Kaprio, 2011). Preliminary studies have so far suggested similar chromosomal regions relating intelligence to reading (Luciano et al., 2006; Posthuma et al., 2005) and educational performance (Wainwright et al., 2006). Such findings would require replication however if they were to be validated, and a persistent challenge to molecular genetics research is the need for massive databases to achieve adequate statistical power in detecting small effects, of what are likely to be several implicated genes (Fisch, 2009). A recent approach to assessing the phenotypic variation and covariation between traits, in respect of genetic influence, is Genome-wide Complex Trait Analysis or GCTA (Yang, Lee, Goddard, & Visscher, 2011) that uses genetic data from unrelated individuals (as cited previously in Davies et al., 2011). This new method overcomes the sample-size limitations imposed by family-recruitment based studies.

Conclusion

The observation of strong additive genetic covariance between intelligence test scores and academic achievements in two large national cohorts of elementary schoolchildren is consistent with previously reported estimates from self- and/or preselected twin study samples. The twin selection and analytic methods employed in this chapter, and the previous one, may therefore prove useful for other multivariate behaviour genetics studies using data from large representative groups in the absence of pedigree information.

Table 4.1 Descriptive statistics, and intraclass correlations of OS and SS twin pairs: The Netherlands.

	Mean (SD)[a]			Skew	Kurtosis	*t*	
	Singletons	OS twin members	SS twin members	All	All	OS twin pairs	SS twin pairs
Age 8	*n* = 57,701	*n* = 336	*n* = 842				
IQ	0.00 (1.00)	0.03 (1.01)	0.10 (0.96)	-0.53	-0.28	0.30	0.42
Language	0.00 (0.99)	0.05 (0.99)	0.06 (0.97)	0.13	0.28	0.32	0.53
Arithmetic	0.00 (0.99)	0.03 (0.95)	0.04 (1.02)	0.23	0.03	0.30	0.48
Age 10	*n* = 54,027	*n* = 300	*n* = 694				
IQ	0.01 (0.96)	0.06 (0.97)	0.05 (0.91)	-0.61	-0.03	0.36	0.43
Language	-0.03 (0.93)	0.07 (0.92)	0.02 (0.91)	0.18	-0.15	0.35	0.45
Arithmetic	-0.01 (0.95)	-0.01 (0.95)	0.00 (0.93)	-0.03	-0.15	0.33	0.51
Age 12	*n* = 51,531	*n* = 264	*n* = 594				
IQ	0.00 (1.00)	0.05 (0.98)	0.06 (0.96)	-0.50	-0.30	0.31	0.51
Language	0.00 (1.00)	0.12 (1.06)	0.10 (0.97)	0.21	0.04	0.34	0.48
Arithmetic	0.00 (0.99)	0.04 (0.98)	0.07 (0.93)	-0.02	-0.20	0.47	0.56

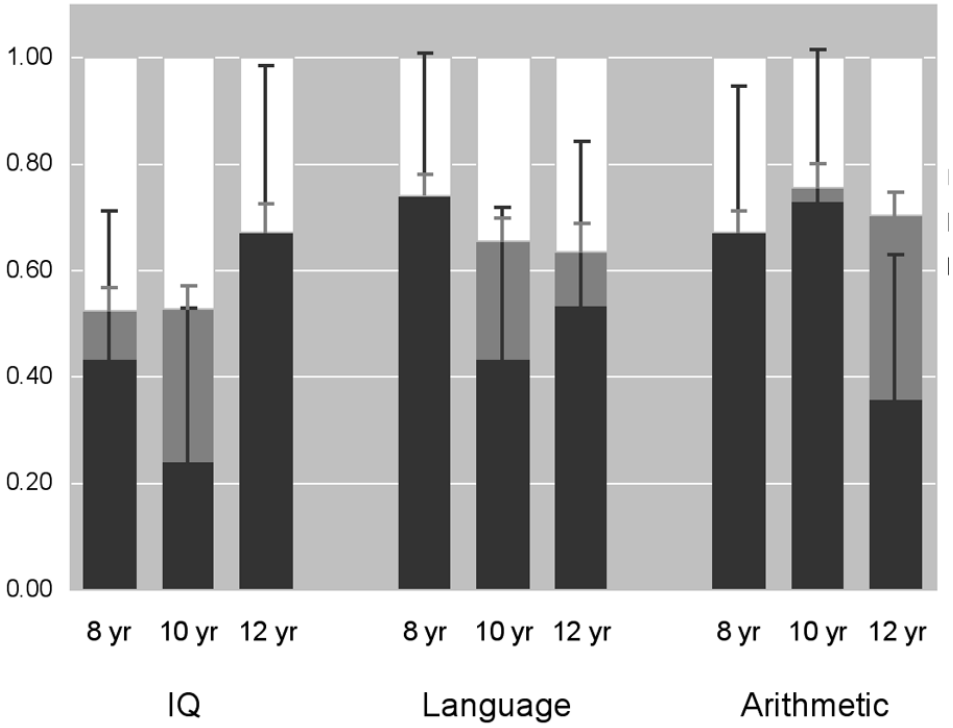
Note. IQ = intelligence quotient; OS = opposite sex; SS = same sex; *t* = intraclass correlation.
[a] ANOVA resulted in no statistically significant group differences on the assessments, with two exceptions: IQ at age 8 ($F = 4.336$, $p = .013$), with twins performing slightly above singletons in post-hoc tests ($t = 1.919$, $p = .055$); language performance at 12 years ($F = 5.514$, $p = .004$), with twins again performing above singletons ($t = 3.059$, $p = .002$).

Table 4.2 Bivariate genetic and shared environment correlations (and standard errors): The Netherlands.

	IQ, 8 yrs		IQ, 10 yrs		IQ, 12 yrs	
	r_G	r_C	r_G	r_C	r_G	r_C
Language	0.82 (*0.26*)	- (-)	0.31 (*0.45*)	0.74 (*0.56*)	0.50 (*0.28*)	- (-)
Arithmetic	0.37 (*0.27*)	- (-)	0.44 (*0.39*)	1.79 (*3.02*)	0.58 (*0.29*)	- (-)

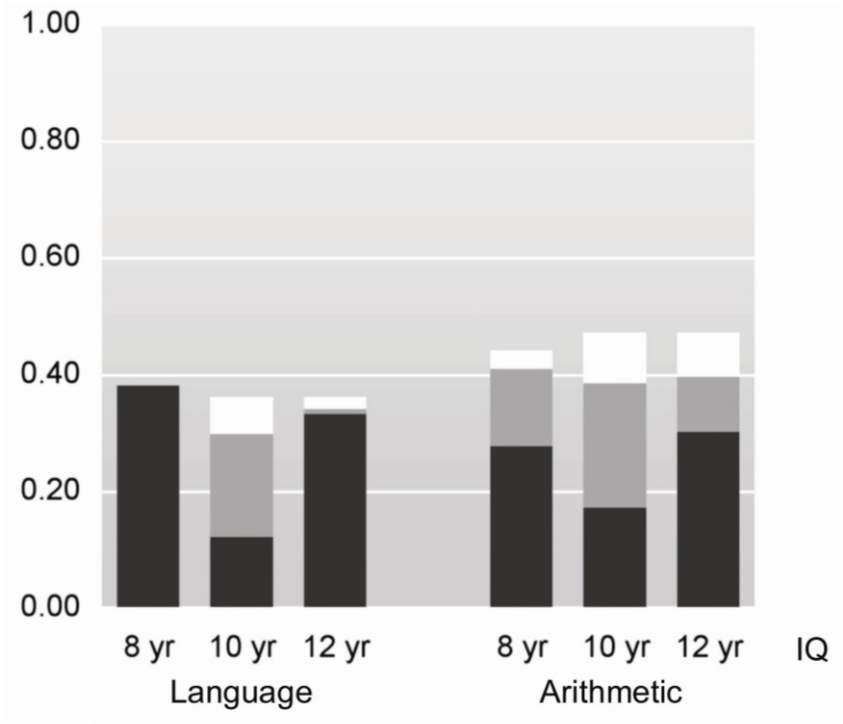
Note. IQ = intelligence quotient, r_G = genetic correlation, r_C = shared environment correlation
Standard errors were not estimable for shared environmental correlations between IQ and education variables at 8 and 12 years, due to close-to-zero variance components and relatively large standard errors in IQ at age 12, and language and arithmetic at age 8

Figure 4.1 Univariate estimates of additive genetic, shared and unique environment effects on intelligence and academic achievement: The Netherlands.



Note. Bar shadings indicate the proportions of additive genetic (h^2; black), shared environment (c^2; grey), and unique environment (e^2; white) effects; error bars show the standard errors for h^2 and c^2. IQ = intelligence quotient.

Figure 4.2 Covariance estimates of additive genetic, shared and unique environment effects: The Netherlands.



***Biv h*^{2}**	1.00	0.33	0.92	0.63	0.36	0.64
***Biv c*^{2}**	0.00	0.49	0.02	0.30	0.45	0.20
***Biv e*^{2}**	0.00	0.18	0.06	0.07	0.18	0.16

Note. The covariances for the different age groups are with IQ. Bars represent phenotypic correlations and their shadings indicate their relative proportions due to additive genetic (black), shared environment (grey), and unique environment (white) effects. Values beneath the bars correspond to the covariance estimates for additive genetic (*Biv* h^2), and shared (*Biv* c^2) and environmental effects (*Biv* e^2), which when summed together equal 1.0.

Chapter 5
Childhood intelligence and midlife inflammatory and haemostatic biomarkers: The 1958 National Child Development Study

Chapter 1 outlined evidence for the relationship between higher childhood cognitive ability and reduced cardiovascular disease (CVD) risk found in prospective longitudinal studies of large nationally representative cohorts (Batty, Mortensen, Andersen, et al., 2005; Batty, Shipley, Mortensen, Gale, et al., 2008; Deary, Whiteman, Starr, Whalley, & Fox, 2004; Lawlor et al., 2008). Whereas the mechanistic pathways for this association are not yet well understood, associations between intelligence and either constitutional and/or modifiable risk factors for CVD can reveal potential causal pathways, ultimately leading to testing hypotheses central to cognitive epidemiology (Deary, 2008). This chapter investigates the association between psychometric intelligence in youth and emerging CVD-risk biomarkers, at an age in adulthood before the onset of the majority of CVD-related morbidities. Using a nationally representative cohort from the UK, it also considers confounding and mediation effects on this behaviour-to-biology pathway.

Psychometric intelligence and conventional CVD risk factors

Childhood intelligence is inversely associated with adult blood pressure (BP), body mass index (BMI), blood triglycerides, obesity, blood glucose, and smoking (Starr et al., 2004; Batty, Gale et al., 2008; Der et al., 2009; Power, Jeffries, & Manor, 2010; Richards et al., 2009; Chandola et al., 2006; Batty, Deary, & Macintyre, 2007; Batty, Deary, Schoon, & Gale, 2007b; Taylor et al., 2003). This evidence largely comes from substantial longitudinal study cohorts from the UK and US. A moderate degree of the forward association between psychometric intelligence and CVD-morbidity is shown to be via clusters of physiological CVD risk factors (Batty, Shipley, Mortensen, Gale, et al., 2008; Wennerstad, Silventoinen, Tynelius, Bergman, & Rasmussen, 2010). Behavioural risk factors for CVD, such as smoking,

count among some of the more substantive of mediators in the pathway, so far reported (Batty, Shipley, Mortensen, Gale, et al., 2008). However, looking outside conventional risk factors for CVD may help to explain additional variance in the effect of premorbid cognition on later vascular health.

Premorbid cognition and systemic inflammation

Recently two inflammatory biomarkers of CVD risk—C-reactive protein (CRP) and fibrinogen—that have been inversely associated with later adult cognitive function (Gimeno, Marmot, & Singh-Manoux, 2008; Komulainen et al., 2007; Teunissen et al., 2003) and positively associated with cognitive decline (Marioni, Strachan, et al., 2010; Rafnsson et al., 2010; Hoth et al., 2008), were also found to be inversely associated with premorbid intelligence. In a prospective cohort study, cognitive ability test scores at age 11 years accounted for much of the cross-sectional association between lower cognitive performance and higher CRP and fibrinogen levels at age 70 years (Luciano et al., 2009). This provided evidence of possible reverse causation in the inflammation-to-cognition pathway. It also raised, for the first time, the possibility that such biomarkers are potential mediators on a pathway linking childhood intelligence to CVD risk.

The intention of the present chapter's investigation of associations between childhood intelligence and emerging adult CVD biomarkers is not only to consider the likelihood of reverse causation in a younger cohort (cf. Luciano, 2010), but also to contribute to an understanding of causal mechanisms in cognition and vascular health outcome associations. The biochemical survey of the National Child Development Study (NCDS) of 1958 (Power & Elliot, 2006) provides data on circulating inflammatory and haemostatic biomarkers of 45 year-olds—34 years after their completion of intelligence-type assessments. Among these biomarkers is CRP, an acute-phase protein and major inflammatory CVD biomarker with variance showing in healthy populations (Ridker, 2009). Elevated CRP has been associated with the increased risk of ischaemic stroke, peripheral arterial and coronary heart diseases, diabetes, hypertension, more severe outcome following heart attack, and death (Danesh, Collins, Appleby, & Peto, 1998; The Emerging Risk Factors

Collaboration, 2010). The other low-grade inflammatory biomarker included in the survey is fibrinogen. This shows biological dependency with CRP, but it may be an independent risk marker for CVD due to its haemostatic properties, relating to platelet adhesion and aggregation, and fibrin formation (The Fibrinogen Studies Collaboration, 2007). Such mechanisms are involved in cerebrovascular disease, providing a rationale for the study of fibrinogen in relation to cognitive function (Luciano et al., 2009).

Cognition and haemostasis

The remaining biomarkers in the present study, d-dimer, tissue plasminogen activator (t-PA) antigen, and von Willebrand Factor (VWF) antigen, that are also indicators of haemostasis, are less routinely tested as CVD-risk indicators and perhaps for this reason their association with cognitive function has remained relatively unexplored. However, they are each independent biomarkers of specific CVD-type risk, in either healthy or clinical populations (Danesh et al., 2001; Lowe et al., 2004; Spiel, Gilbert, & Jilma, 2008; Woodward, Rumley, Welsh, MacMahon, & Lowe, 2007), and are therefore, in the context of the present study, worthy of investigation in association with premorbid intelligence. D-dimer, a marker of coagulation activation, has shown association with cognitive decline in older adults (Stott et al., 2010). However, whether the remaining two haemostatic measures relate to cognition remains hypothetical. VWF antigen is a blood plasma glycoprotein, which is a marker of endothelial disturbance, and plays a role in platelet aggregation and adhesion. It is particularly informative for existing CVD, rather than being predictive at a preclinical stage (Spiel et al., 2008). The glycoprotein t-PA antigen—another marker of endothelial disturbance, and a major mediator of fibrinolysis—is predictive of increased CHD risk in healthy populations (Lowe et al., 2004).

The present study

In the present study the NCDS 1958 cohort data are used to assess:

1. The association between age 11 cognitive test scores and CVD biomarker levels in midlife, at an age before the risk of confounding by existing somatic disease considerably increases, and before the problem of survival bias.
2. Potential confounding of this association by early life factors.
3. Mediation pathways via established CVD risk factors in adulthood.

In a recent study from the NCDS 1958 cohort, socioeconomic position in early life was associated with inflammatory and haemostatic markers in midlife; that is, higher occupational grades of the child's parents conferred protection by their association with lower levels of these CVD biomarkers (Tabassum et al., 2008). Therefore, it is possible that any inverse association between premorbid intelligence and biomarker status is indirect and non-causal (Marioni, Deary, et al., 2010) if, for example, it is confounded by early life social inequalities. Tabassum et al (2008) reported that the accumulation of lifetime SES was a better predictor of blood biomarkers than either child or adult SES alone, and which was largely accounted for by health behaviours. Therefore, the present study adjusts for both early life and adult SES to assess the extent to which, respectively, they may confound or mediate the association between premorbid cognition and midlife inflammation and haemostasis.

If mediation is a likely explanation for the forward association between cognition and biomarker status, then adjustment for CVD-risk factors, other than SES, should be made. It has been proposed that such mediation could either occur via vascular processes, or behavioural factors to do with lifestyle and health literacy, including smoking (Marioni, Deary, et al., 2010). If conventional CVD risk factors that relate to inflammation and haemostatic status are also associated with premorbid intelligence scores, this makes them likely candidates as potential mediating factors. Among the conventional risk factors that have been associated with psychometric intelligence in youth, body mass index (BMI), blood pressure, waist-to-hip ratio (WHR), and smoking, also show positive and significant associations with the inflammatory markers CRP and fibrinogen (Hamer & Stamatakis, 2008; Kaptoge et al., 2007; Nguyen, Lane, Smith, & Nguyen, 2009); therefore, in addition to adult SES mediation effects are tested by adjusting for these four risk factors.

Finally, with the availability of cognitive performance scores at age 50, the present study also has the opportunity to test:

4. Potential reverse causation in the assumed forward association between midlife biomarkers and adult cognitive function, by controlling for childhood intelligence.

Particular attention is paid to associations between each of the biomarkers, and specific cognitive test domains in adulthood. This is because of evidence that CVD-morbidity types relate to specific cognitive functions, rather than a general cognitive ability (Verhagen, Borchelt, & Smith, 2003). In the present cohort relationships are investigated between midlife biomarkers and verbal short-term memory, processing speed, and verbal fluency, while controlling for childhood intelligence.

Methods

Study population

Participants of the NCDS 1958 cohort, who were born in the UK during a single week in March 1958, were traced longitudinally to 2008 (Power & Elliot, 2006). This is an ongoing longitudinal study that emanated from the Perinatal Mortality Survey of over 17,000 newborns, which at that time collated medical data from midwives' records, and social and demographic information from mothers. Up to 2008 there were 8 sweeps of data collection following baseline, at ages 7, 11, 16, 23, 33, 42, 46 and 50 years. Among 14,132 who had cognitive test scores at age 11 years, 11,419 completed health and social questionnaires at age 42 and, of these, 9,377 returned for a biomedical survey at age 45 that included the collection of blood samples, constituting 66% of the 11-year-old cohort, and 55% of the original perinatal survey. The adult cognitive battery taken at age 50 (described below), involved 8,078 (86.1%) of those with blood-derived data.

Cognitive ability at 11 and 50 years

Childhood intelligence was assessed with a test devised by the National Foundation for Educational Research in England and Wales (Pigeon, 1964). Each multiple-choice item requires the correct selection of a missing word or figure from a verbal or abstract sequence. Total scores (out of 80) on this test show high test-retest reliability (r = .94) and validity in relation to educational tests (r = .69 to .93) (Douglas, 1964).

Adult cognitive function was measured with computer assisted personal interviewing (CAPI), across four tests of attention and memory (ESDS, 2012), including: (1) *Word list recall* that involved learning a list of 10 words, each presented by a computerised voice at two-second intervals; the participant was scored on the number of words correctly recalled; (2) *Delayed word recall*, again scored out of 10, which was presented at the end of the cognitive test battery, and required recall of as many words from the original word list as possible; (3) *Verbal fluency*, which allowed one minute for the participant to name as many different animal species as possible. This task shows high test-retest reliability (r = .70) and positive correlations with vocabulary (r = .33) and word recognition tasks (r = .36) (Lang, Weiss, Stocker, & von Rosenbladt, 2007). And finally: (4) *Visual processing speed* was measured using a letter cancellation task, in which the participant was given one minute to cross out as many Ps and Ws from a randomly generated list of alphabet letters. Although speed and accuracy scores were recorded separately for this fourth task, the total number of correctly marked letters was used for the present study's analysis (scored out of 65). Due to disruption of the testing environment affecting 688 participants' scores (7.1%), according to the interviewers, these were excluded from the analysis.

Inflammatory and haemostatic biomarkers

Non-fasting venous blood samples were centrifuged for plasma, which was analysed for inflammatory and haemostatic biomarkers. These included: (1) *CRP*, (2)

fibrinogen, (3) *D-Dimer*, (4) *t-PA antigen*, and (5) *VWF antigen.* The methods for measuring these have been described elsewhere (Rudnicka, Rumley, Lowe, & Strachan, 2007). Associations among the biomarkers were all positive and reached the 95% level of statistical significance ($0.56 > r > 0.15$) with the exception of D-dimer and t-PA where there was no association (see Appendix C for correlations). A data reduction technique was considered in order to produce a general inflammatory/haemostatic factor. However, the internal consistency among the biomarkers was inadequate (Cronbach's $\alpha = 0.48$), and principal components analysis did not suggest a clear general biomarker factor. Therefore the individual inflammatory and haemostatic measures were retained for analyses, and their statistical non-independence is acknowledged and considered in the interpretation of results.

Covariates and CVD risk factors

Gestational period (day) and *birth weight* (ounce) from medical records were included in the analyses as potential early life indicators of 'system integrity' (Whalley & Deary, 2001), which might contribute to the covariance between individual differences in cognitive ability and biomarkers for CVD. *Background socioeconomic status* (SES)—also recorded at birth—was based on the highest occupational grade of the household, and was also included in the analysis to take account of potential confounding. This was coded according to the 1951 General Register Office: professional (I), intermediate (II), skilled (III), partly skilled (IV) and unskilled (V). Values were reversed so that the highest SES score related to the highest professional category.

The remaining covariates were included in models as potential mediators of the tested pathways. *Adult SES* was rated at middle age according to participants' own occupational grades, and these were coded and reverse scored as background SES. *Smoking behaviour* was self-reported at age 42, and rated from 0 to 2 according to the following categories: 'never smoked', 'occasional or ex-smoker', and 'regular current smoker'. The remaining CVD risk factors were measured at age 46, at the time of biomarker testing. Resting *systolic blood pressure* (BP) and *diastolic BP*

were measured three times each, and the average of these six readings were used; the mean of systolic and diastolic BP has been found to be a better predictor of CVD than either one alone (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002). *Body mass index* (BMI) and *waist-to-hip ratio* (WHR) were estimated with the following formulae:

BMI = weight (kg) / height (m^2)

WHR = waist circumference (cm) / hip circumference (cm)

Statistical analysis

Variable treatment

Childhood and adult cognitive test scores approximated a normal distribution, and were standardised for the purposes of analyses (M = 0, SD = 1). As childhood verbal and nonverbal scores were similar in their associations with the biomarkers, and they correlated highly (r_s = .79), their combined score only was retained. All biomarker measures were significantly positively skewed, and were log-transformed, although descriptive data of raw scores are reported in Results. Biomarker outliers were identified beyond three standard deviations above or below the mean, and excluded from all analyses. All other measures followed a normal distribution, including both SES variables (treated as continuous variables in the analyses). One exception was smoking, where the distribution of participants in each subsequent category was positively skewed.

Statistical models

All analyses were carried out using *SPSS version 17.0*. Independent samples *t*-tests and analysis of variance (ANOVA) tested for sex differences in continuous and categorical variables, respectively. Because no significant interaction effects of sex were observed in the large majority of intelligence-biomarker relationships, regression models were run for the total cohort only, and sex was included as a

covariate. After confirming linearity of all bivariate relationships linear regression examined the association between cognitive performance and the biomarkers, in basic and covariate-adjusted models. All covariates were entered as continuous variables. Regression coefficients (unstandardised) are reported with 95% confidence intervals, and squared partial correlations are used to calculate the change of proportion in variance explained from basic to covariate-adjusted models:

$$\text{Partial } r^2_{\text{basic model}} - \text{partial } r^2_{\text{adjusted-model}} / \text{partial } r^2_{\text{basic model}}$$

When such models are compared sample sizes are equal, including only those cohort members with no missing data.

Attrition weight

I included a weighting in each model using the weighted least squares (WLS) regression method to adjust for attrition bias among the follow-up adult cohort, which had above average childhood cognitive scores compared with those of the original cohort (Atherton, Fuller, Shepherd, Strachan, & Power, 2008). For example, among those who responded to the biomedical survey, childhood IQ performance was on average 5.8 points higher than among those 11-year-olds lost to follow-up (t = -21.3, Cohen's d = -0.37, $p < .001$). This weighted variable, calculated from logistic regression, represents the inverse probability of responding to the biomedical survey at age 45, as predicted by each respondent's sex and childhood cognitive test score. In models where adult cognitive function was the outcome variable, the weighting was the reciprocal probability of having a cognitive test score at age 50, as predicted by childhood IQ and sex.

Results

Child and adult characteristics of the cohort appear in Table 5.1. Sex differences are highlighted where they were statistically significant ($p < .05$). Female

members of the cohort scored on average 2.3 points above male members on cognitive ability at age 11 (t = -6.78, Cohen's d = -0.15, $p < .001$). In adulthood there were no significant sex effects on cognitive performance. In midlife, women had higher mean levels of the biomarkers CRP, fibrinogen and D-dimer, and men showed higher mean values for t-PA antigen and VWF antigen (sex differences were all statistically significant at $p < .01$).

Childhood intelligence and adult inflammation, haemostasis

Table 5.2 presents regression coefficients from basic models (adjusted for sex) and covariate-adjusted models, of the association between childhood intelligence and midlife biomarkers. In basic models a one *SD* advantage in childhood intelligence was associated with significantly lower levels of the five inflammatory and haemostatic biomarkers at midlife. The effect size (partial correlation) for this inverse association was greatest for childhood cognition and CRP (partial r = -0.13), or childhood cognition and fibrinogen (partial r = -0.14), as compared with the other three biomarkers: T-PA antigen (partial r = -0.08), VWF antigen (partial r = -0.08), and D-dimer (partial r = -0.07). A one *SD* increase in IQ was associated with a decrease of 1.08 mg/L CRP (non-log transformed value).

The inclusion of early life factors to the models reduced the childhood intelligence-biomarker associations by 24 to 44%, although these models remained statistically significant (coefficients = -0.058 to -0.007, partial r = -0.10 to -0.04, $p <$ 0.05). Early life SES had by far the greatest influence on this attenuation effect, as compared with birth weight and gestational age (results not shown but available upon request).

Further adjustment for multiple adult CVD risk factors reduced the childhood intelligence-biomarker gradients by 82 to 100%, and age-11 cognition was no longer statistically significant in predicting D-dimer, VWF antigen and t-PA antigen. In models that adjusted for each of the adult risk factor covariates individually, no single factor consistently better explained the cognition-biomarker association than the combined cluster of factors. However, BMI, SES, smoking and WHR each attenuated the basic models by 50 to 100% for each of the five biomarkers, whereas

adjustment for BP had a lesser effect, reducing the magnitude of the associations by a quarter to a half.

Inflammation-Cognition in midlife: Reverse causation?

Table 5.3 presents beta coefficients from models relating adult biomarker levels with adult cognitive test performance. In basic models (Model 1) inverse associations were observed; that is, higher inflammatory and haemostatic markers at age 45 were related to significantly poorer cognitive performance on the attention and memory tasks at age 50. The effect sizes (as partial correlations) were as follows: CRP (partial r = -.02 to -.09), fibrinogen (partial r = -.02 to -.09), D-dimer (partial r = -.03 to -.06), VWF antigen (partial r = -.03 to -.07), and t-PA antigen (partial r = -.01 to -.04). These were statistically significant associations with the exception of t-PA antigen with the Letter cancellation and Word recall tasks, and CRP and fibrinogen with Letter cancellation. After adjustment for childhood intelligence (Model 2) the biomarker-to-adult-cognition associations were substantially reduced. The association between inflammatory biomarkers and adult cognitive function, after controlling for childhood intelligence, was altered by between two-thirds to full attenuation (CRP, 71 to 90%; fibrinogen, 67 to 98%). The association between the different haemostatic biomarkers and adult cognition showed attenuation effects of half or more after adjustment for childhood intelligence.

To consider the independent associations of inflammation and haemostasis with later cognitive function, the blood biomarkers were entered simultaneously in to models to predict adult cognitive test performance, whilst controlling for childhood intelligence (data not shown). In these models, the haemostatic marker D-dimer maintained a statistically significant association ($p < 0.05$) with the verbal recall task, and VWF antigen remained significantly predictive of the verbal fluency and delayed word recall tasks ($p < 0.05$). Among the inflammatory markers, CRP and fibrinogen remained significantly predictive of immediate and delayed verbal recall respectively, after controlling for all other biomarkers and childhood intelligence.

Discussion

Childhood cognitive ability is inversely associated with levels of five low-grade inflammatory and haemostatic CVD risk factors measured 34 years later. These statistically significant associations show small effect sizes, yet they may still have clinical relevance. For example, if a CRP level above 3 mg/L indicates double the risk of coronary heart disease compared to <1 mg/L in adult populations (Pearson et al., 2003), then the decrease of 1.08 mg/L in association with a one standard deviation increase in intelligence test scores, observed in the present study, is not trivial. The magnitude of the intelligence associations with CRP and fibrinogen are similar to those from the only other study so far to investigate this longitudinal relationship (Luciano et al., 2009). The observed associations between cognitive ability in youth, and adult D-dimer, t-PA antigen and VWF antigen, which were also statistically significant, are novel and require replication.

Evidence for behavioural mediation, not confounding

Early life SES, as measured by parental occupation, which correlates with cognitive ability (Deary et al., 2005) and has previously shown inverse associations with the present study's biomarkers (Tabassum et al., 2008), did not adequately explain the association. This is consistent with studies reporting a minimal degree of confounding by childhood SES in either intelligence-biomarker (Karlsson, Ahlborg, Dalman, & Hemmingsson, 2010) or intelligence-CVD associations (Batty, Mortensen, Andersen, et al., 2005; Batty, Wennerstad, et al., 2009; Wennerstad et al., 2010), albeit that relatively larger attenuation effects were observed than these studies. Instead, the relation of childhood intelligence and adult biomarkers was more likely explained by mediation from lifetime health behaviours—or indicators of these—that are among established CVD risk factors. After controlling for these individually and collectively, intelligence-biomarker associations were substantially reduced. These considerable attenuations are consistent with those from studies that have controlled for multiple CVD risk factors in associations between childhood intelligence and CVD morbidity (Batty, Shipley, Gale, et al., 2008), and biomarkers

and later cognitive function (Luciano et al., 2009). A mediation effect of WHR in the present study, for example, could indicate that lower childhood intelligence is related to a reduction in physical activity and poorer dietary choices (Batty, Deary, Schoon, & Gale, 2007a), leading to excessive inflammatory and/or haemostatic status (Giugliano, Ceriello, & Esposito, 2006; Kasapis & Thompson, 2005) if, indeed, WHR is more strongly influenced by lifestyle behaviours than genetic factors. Similarly, smoking that has previously been related to lower premorbid intelligence (Batty, Deary, & Macintyre, 2007; Batty, Deary, Schoon et al., 2007b; Taylor et al., 2003)—and which in the present study reduced up to half of the variance in the intelligence-biomarker associations—could be a mediating factor via inflammation or blood viscosity (Ambrose & Barua, 2004). However, as adult CVD risk factors were assessed at a similar age to the biomarkers in the present study, there is a limit to the inferences one can make about directions of causation among these variables. The substantial attenuation effects observed after adjusting for adult SES are consistent with studies that control for adult SES indicators in models relating premorbid intelligence to all-cause mortality (Lawlor et al., 2008; Jokela, Elovainio, Singh-Manoux, & Kivimaki, 2009; Jokela, Batty, Deary, Gale, & Kivimaki, 2009; Kuh et al., 2009). However, in this case, there is the possibly of overadjustment due to the significant covariance between cognitive and socioeconomic indicators.

Alternative explanations for unexplained variance

An alternative explanation for intelligence-biomarker associations could be the presence of a shared antecedent factor, consistent with the system integrity hypothesis (Deary, 2008). For example, a biological predisposition towards increased systemic inflammation, either genetically determined and/or realised at conception (Marioni, Strachan et al., 2010), may underlie an indirect association between cognitive and vascular processes. This is an interesting possibility, given the inverse association between premorbid intelligence and other adult conditions including depression and diabetes (Der et al., 2009; Gale et al., 2008), which share in common higher circulating inflammatory markers compared to control groups (Dehghan et al., 2007; Leonard, 2007); it is also plausible given the high heritability estimates of

intelligence test scores (Plomin et al., 2009) and CRP, and fibrinogen levels respectively (Su et al., 2008). The five biomarkers reported in the present chapter are either directly or indirectly linked to inflammatory processes (Woodward et al., 2007), and show a degree of biological dependency. However, as they can also show biological variation (Rudez et al., 2009) it is unclear if their significant associations with childhood intelligence in the present study were due to inflammatory factors alone, or whether haemostatic factors are independently related, perhaps due to their association with neuronal blood flow. Haemostatic biomarkers are risk markers for CVD (Woodward et al., 2007; Danesh et al., 2001), vascular dementia, Alzheimer's disease (Gallacher et al., 2010; van Oijen, Witteman, Hofman, Koudstaal, & Breteler, 2005) and peripheral atherosclerosis (Tzoulaki et al., 2006), even after controlling for the effects of circulating inflammation (Woodward et al., 2007), and I found evidence for independent associations between haemostatic markers and later cognitive function, after adjusting for inflammatory biomarkers. Still, childhood intelligence in the present study explained a greater proportion of variance in the inflammatory biomarkers compared with those directly related to haemostatic function. Exploring a genetic linkage between systemic inflammation and cognition is therefore a worthwhile endeavour, despite that, in the largest study to date, genetic variants associated with inflammatory biomarkers were not found to relate to childhood intelligence (Marioni, Deary et al., 2010).

Strengths and limitations

Among the strengths of the present study are its large nationally representative cohort and the substantial follow-up period. Given access to childhood cognitive data on those individuals lost to follow-up by midlife, I was able to control for potential attrition bias in the models with the use of weighting, to derive effect sizes that may be more generalisable to the background population. The measurement of biomarker data at midlife, compared to older age in the only other previous study (Luciano et al., 2009), means that a greater proportion of people at risk for CVD were likely captured, but before disease onset, giving temporal precedence to biomarkers on a pathway linking intelligence and CVD risk

(O'Connor et al., 2009) (although testing such mediation effects is out with the design of the present study). The inclusion of adult cognitive performance scores in this cohort study gives further exposure to the possibility of reverse causation in inflammation-to-cognition associations reported in the cognitive ageing literature, while also indicating specific cognitive functions (for example, verbal memory) that may be affected by inflammatory and haemostatic status once premorbid intelligence is taken account of.

The present study has a few main design limitations that must be addressed here. First, in the absence of inflammatory and haemostatic biomarker data from childhood, causal inferences are more limited about pathways linking childhood intelligence to adult biomarker status. In a previous cross-sectional cohort study of young healthy adult men, intelligence test scores inversely related to erythrocyte sedimentation rate (Karlsson et al., 2010)—an indirect measure of fibrinogen (Batlivala, 2009)—at an age before adverse health behaviours may have become established lifetime behavioural patterns that greatly increase CVD risk. To control for baseline CVD biomarker status in the present study would have been to elucidate more clearly the directions of association between cognitive function and biomarker status. Second, adjustment for childhood intelligence in associations between CVD biomarkers and adult cognition was limited by the difference in cognitive test batteries administered in youth and adulthood. In a previous study (Luciano et al., 2009) the significantly positive association between inflammatory status and cognition in adulthood, which was entirely attenuated after adjustment for a childhood score on the exact same task, was convincing evidence to the field of cognitive ageing research of possible reverse causation. Nevertheless substantial (and sometimes full) attenuation effects were still observed after adjustment for performance on the non-identical cognitive test at age 11, and relationships in which there was relatively less attenuation are areas worthy of future investigation in cognitive ageing. For example, increased D-dimer levels have previously been related to greater cognitive decline among older adults (Stott et al., 2010), independent of inflammatory biomarkers, and the present study support this finding, reporting for the first time on the significant association between this haemostatic

biomarker and verbal memory while controlling for general intelligence in childhood.

Other systemic inflammatory biomarkers were missing from the present study, for example cytokines, which may be stronger predictors of CVD events in older adults than the acute-phase proteins tested in the present study (Ramos, Pellanda, Gue, & Portal, 2009). It is not known, for example, whether adult interleukin-6 status—a cytokine that regulates the synthesis of CRP (Gimeno, Ferrie, et al., 2008)—would show a similar magnitude of association with premorbid intelligence. A consideration of a wider collection of acute-phase proteins and cytokines in relation to individual differences in premorbid cognition may profit this area of research (Luciano, 2010).

The study may also have benefited from a wider range of cognitive tests in adulthood to properly assess the effects of the blood biomarkers on specific cognitive function, while controlling for reverse causation by adjusting for premorbid intelligence. Therefore I was unable, for example, to test for replication of the previously reported positive association between CRP and fibrinogen, and processing speeds (Luciano et al., 2009). However, the present study's finding that these biomarkers, along with D-dimer and VWF antigen, are predictive of verbal memory performance in midlife, after accounting for premorbid cognition, is a novel finding.

Conclusion

The present study emphasises the complex bidirectional associations that may occur between cognitive factors and systemic inflammation and haemostasis. It is highly plausible that intelligence differences in childhood relate to CVD biomarkers by acting via lifestyle behaviours as the present data support, just as it is also likely that changes to systemic inflammation and haemostasis in adulthood will have detrimental effects to specific cognitive processes over time. But whether there is an antecedent factor that carries greater influence in driving intelligence-CVD biomarker associations, relative to the bidirectional causal processes that carry out throughout the life course, remains a challenge for future work to address.

Table 5.1 Descriptive statistics of study variables: 1958 National Child Development Study.

	N	*M*	*SD*
Cognitive measures			
Total cognitive score, age 11	8,126	45.4	*15.4* [a]
Word recall, age 50	6,627	6.7	*1.4*
Verbal fluency, age 50	6,627	22.6	*6.3*
Letter cancellation, age 50	6,528	21.8	*5.8*
Delayed recall, age 50	6,581	5.6	*1.8*
Biomarkers, age 45			
CRP (mg/L)	6,660	2.1	*3.2* [a]
Fibrinogen (g/L)	6,621	2.9	*0.6* [a]
D-dimer (ng/mL)	6,563	183.4	*112.0* [a]
t-PA antigen (ng/mL)	6,625	5.2	*2.7* [b]
VWF antigen (IU/dL)	6,648	122.4	*40.3* [b]
Covariates			
Gestation (day)	7,051	281.2	*11.8*
Birth weight (ounce)	7,542	117.8	*18.0* [b]
BMI (kg/m^2)	7,980	27.3	*4.9* [b]
WHR (cm)	8,059	0.9	*0.1* [b]
BP (mm hg)	7,908	101.0	*15.5* [b]
		Percent (%)	
Childhood SES, low to high	6,454	12.8; 15.2; 52.0; 16.7; 3.2	
Adult SES, low to high	7,769	3.6; 12.8; 41.4; 37.0; 5.3 [c]	
Smoking, never; occasional; current	7,874	46.0; 29.8; 24.3	
Sex, female	4,095	50.4	

Note. BP = mean blood pressure [systolic + diastolic / 2]; BMI = body mass index; CRP = C-reactive protein; SES = socioeconomic status; t-PA = tissue plasminogen activator; VWF = von Willebrand factor; WHR = waist-hip ratio.
[a] Significantly higher *M* for female versus male groups, $p < .001$
[b] Significantly higher *M* for male versus female groups, $p < .01$
[c] A greater proportion of men than women were in the higher SES groups (Pearson's $\chi^2 = 210.5$, $p < .001$).

Table 5.2 Regression coefficients (and 95% CI) for associations between childhood intelligence and adult blood biomarkers.

	CRP *N* = 4,245		Fibrinogen *N* = 4,219		D-dimer *N* = 4,183		t-PA antigen *N* = 4,226		VWF antigen *N* = 4,235	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Model 1[a]	-0.069	(-0.086 , -0.053)***	-0.011	(-0.014 , -0.008)***	-0.011	(-0.018 , -0.004)**	-0.014	(-0.021 , -0.007)***	-0.008	(-0.013 , -0.004)***
Model 2	-0.058	(-0.074 , -0.041)***	-0.010	(-0.013 , -0.007)***	-0.009	(-0.016 , -0.001)*	-0.011	(-0.018 , -0.003)**	-0.007	(-0.012 , -0.002)**
Model 3	-0.023	(-0.039 , -0.007)**	-0.004	(-0.007 , -0.001)**	0.000	(-0.008 , 0.007)	0.004	(-0.003 , 0.012)	-0.002	(-0.007 , 0.003)

Note. The beta coefficient represents a one *SD* advantage in childhood intelligence associated with a unit decrease in the log transformed biomarker value. Asterisks indicate statistically significant models, *$p < 0.05$; **$p < .01$; ***$p < .001$. The changes in the *F* statistic from Models 1 to 2 and Models 2 to 3 are all statistically significant ($p < .05$).

[a] Model 1 is the basic model adjusting for sex and weighted for attrition; Model 2: Basic model + early life factors (gestation, birth weight and childhood socioeconomic status; Model 3: Model 2 + adult covariates (adult socioeconomic status, mean blood pressure, body mass index, smoking and waist-to-hip ratio)

Table 5.3 Regression coefficients (and 95% CI) for associations between adult blood biomarkers and cognitive performance after 5 years.

		Word recall	Delayed recall	Verbal fluency	Letter cancellation
	Model [a]	B 95% CI	B 95% CI	B 95% CI	B 95% CI
CRP	1	-0.169 (-0.221 , -0.118)***	-0.148 (-0.199 , -0.097)***	-0.128 (-0.180 , -0.076)***	-0.039 (-0.090 , 0.012)
	2	-0.088 (-0.138 , -0.039)***	-0.066 (-0.115 , -0.017)**	-0.041 (-0.090 , 0.009)	0.014 (-0.036 , 0.064)
Fibrinogen	1	-1.066 (-1.379 , -0.753)***	-1.096 (-1.407 , -0.784)***	-0.840 (-1.158 , -0.522)***	-0.282 (-0.593 , 0.028)
	2	-0.584 (-0.886 , -0.283)***	-0.607 (-0.905 , -0.309)***	-0.322 (-0.626 , -0.018)*	0.036 (-0.271 , 0.343)
D-dimer	1	-0.255 (-0.376 , -0.135)***	-0.167 (-0.287 , -0.047)**	-0.153 (-0.275 , -0.031)*	-0.150 (-0.269 , -0.031)*
	2	-0.157 (-0.272 , -0.043)**	-0.068 (-0.182 , 0.045)	-0.049 (-0.164 , 0.067)	-0.086 (-0.203 , 0.031)
t-PA antigen	1	-0.092 (-0.210 , 0.027)	-0.102 (-0.220 , 0.016)	-0.182 (-0.302 , -0.061)**	-0.057 (-0.174 , 0.061)
	2	0.022 (-0.091 , 0.135)	0.014 (-0.098 , 0.125)	-0.062 (-0.176 , 0.052)	0.015 (-0.100 , 0.131)
VWF antigen	1	-0.414 (-0.600 , -0.229)***	-0.494 (-0.678 , -0.310)***	-0.425 (-0.613 , -0.237)***	-0.192 (-0.375 , -0.009)*
	2	-0.253 (-0.430 , -0.076)**	-0.332 (-0.507 , -0.157)***	-0.255 (-0.433 , -0.076)**	-0.089 (-0.268 , 0.091)

Note. CRP = C-reactive protein, t-PA = tissue plasminogen activator, VWF = von Willebrand factor.
All models adjust for sex, and include sample sizes in the range: N = 5,327 to 5,489 (Model 1 and Model 2 are matched on sample size). The regression coefficient is the effect of a one unit increase in the log transformed biomarker value in relation to a one *SD* decrease in the adult cognitive variable; 95% CI are in parentheses. Asterisks indicate statistically significant models, *p < 0.05; **p < .01; ***p < .001. The change in the F statistic from Model 1 to Model 2 is statistically significant in each case.
[a] Model 1 is the basic model that weights for attrition; Model 2 is the basic model adjusted for childhood intelligence.

Chapter 6
Direction of association between cognitive reaction times and systemic inflammation: West of Scotland Twenty-07

Introduction

My basis for the empirical study in Chapter 5 was the observation, from several nationally representative cohorts, of a significant inverse association between premorbid intelligence test performance and adult risk of cardiovascular disease morbidity or related-mortality, with the strength of association greater for coronary heart disease than stroke according to current evidence (Calvin, Batty, & Deary, 2011). The chapter explored biological mechanistic pathways of the association that have so far not been well understood. I found that intelligence in childhood relates to several inflammatory and haemostatic biomarkers, albeit the associations are small. That this biological mechanism should explain a significant degree of variance in the association between cognitive function in youth and later risk of vascular-related health problems may be indicative of mediation by lifestyle behaviours, whereby people with lower cognitive abilities tend later to have more inflammation. An alternative proposition is that of system integrity (Deary, 2008). It is possible that these two influences coexist. The present chapter seeks to investigate further the potential likelihood of a system integrity explanation, alongside lifetime influences, in the pathway from cognitive ability to later inflammatory and haemostatic status. It does this using a different cohort that has used cognitive reaction times rather than psychometric intelligence at baseline, as these measures bear a closer association to neuronal integrity, and importantly, are less confounded by educational and socioeconomic influence.

Processing speed: A step closer to neuronal integrity

The system integrity hypothesis (Deary, 2008) would assert that the association between IQ-type test scores and CVD risk is primarily driven by a shared antecedent biological trait. That is, the population covariance between neuronal

system integrity—measured using cognitive testing by proxy—and blood biomarkers of the inflammatory system, has a biological (and likely genetic) basis. The empirical testing of such hypotheses in cognitive epidemiology and the interpretation of findings may however be limited by use of the most common cognitive trait measure in cohort studies, the IQ score, or general intelligence factor score, *g*. Whereas there is validity for g as a biological trait and proxy measure of brain integrity—heritability accounts for 50% of its variance in human populations, and more when only adult samples are studied (Davies et al., 2011)—as a psychometric test invention it may be prone to bias and/or confounding by educational and cultural exposures. An alternative cognitive measure widely viewed as a closer proxy measure of neuronal integrity, but perhaps used with less frequency than intelligence tests in large cohort studies, is mental processing speed.

Processing speed vs. psychometric intelligence

Processing speed is commonly operationalised using cognitive-experimental tests, including simple or choice reaction time tasks, or inspection time tasks. Performances on these tests show reliability, with evidence of stability over short- and long-term follow-up for mean speed and intraindividual variability (Deary & Der, 2005; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000). They also show validity by significantly correlating with intelligence scores in population samples (Deary, Der, & Ford, 2001; Deary, Johnson, & Starr, 2010), for which the association is found to be substantively heritable according to behaviour genetics evidence (Luciano et al., 2001). Compared to scores on psychometric intelligence tests, however, processing speed indices may be more valid proxy measures of neuronal integrity and function for a few reasons. First, these lower level functional tasks are more independent of acquired knowledge, and so are less likely to carry the risk of confounding by socioeconomic and/educational background, by comparison with intelligence test performance. This is supported by their weak associations with socioeconomic indicators, including education and occupational class (Anstey, Dear, Christensen, & Jorm, 2005), as compared to relatively stronger associations between IQ test scores and SES variables (Deary, Der, & Ford, 2001).

Second, age trends for the slowing of processing speed (Der & Deary, 2006) tend to run in parallel with normal ageing trajectories of changes and/or loss to neuronal function and structure (Powers, 2011), whereas performance on higher level cognitive reasoning tasks remain intact for longer and are probably less sensitive to subtle neuronal change. In meta-analysis of 91 studies the correlation between age and processing speed was r = .52, compared to a correlation of r = .40 for the association between age and cognitive reasoning ability (Verhaeghen & Salthouse, 1997). More recently in a population-representative sample of 7,130 adults from the United Kingdom Health and Lifestyle Survey, Der and Deary (2006) plotted lifetime trajectories of simple and choice reaction time speeds and intraindividual variances, providing evidence that with increasing age reaction time performance becomes slower and more variable—which has been otherwise termed 'inconsistent' (Hultsch et al., 2000).

Third, imaging studies from the cognitive neuroscience of ageing literature provide empirical evidence that changes in processing speed relate to alterations occurring at the neuronal level, particularly in respect to white matter integrity (Madden, Bennett, & Song, 2009). Specifically, increased white matter integrity is significantly associated with faster (Deary, Bastin, et al., 2006; van den Heuvel et al., 2006) and less variable processing speeds (Fjell, Westlye, Amlien, & Walhovd, 2011; Jackson, Balota, Duchek, & Head, 2012) in non-pathological ageing cohorts of adults. Furthermore, in some studies, processing speed tasks are significantly associated with brain white matter integrity—using local or cross-regional measures—whereas general intelligence scores are not (Gunning-Dixon & Raz, 2000; Penke et al., 2010; Rabbitt et al., 2007). One example comes from a study of 132 healthy older adults in Scotland, reporting that a general component of white matter integrity derived from principal components analysis of measures from eight regional tracts, significantly related to an information-processing speed factor but not a general intelligence factor derived from standardised intelligence tests (Penke et al., 2010). In these studies of older cohorts, of course, somatic disease (e.g. hypertension or CVD) or ageing itself may entirely confound the observed associations between imaging measures of white matter integrity and behavioural processing speed. However, at least one study has reported on significant associations between white matter integrity and processing speed in young healthy adults (Madden et al., 2004), suggesting that processing speed indices may reflect

neuronal integrity throughout the life course. This evidence, along with current understanding that faster information processing speed between brain regions is pivotal to the development of higher level cognitive abilities, means that studying reaction times in the context of cognitive epidemiology is of empirical value.

In this chapter a cohort study is presented which examines the association between processing speed and blood biomarkers of inflammation in three differently aged adult cohorts. Issues such as potential confounding, and age-effects on both parameters, are important points of consideration in the interpretation of findings. Indeed, the findings from measures taken in earlier adulthood may be most reliable in terms of indicating optimal and unbiased neuronal system integrity.

Processing speed in cognitive epidemiology

The use of processing speed in testing hypotheses central to cognitive epidemiology is an underdeveloped area of research. Two studies to date have reported on the association between experimental processing speed and risk of death in longitudinal cohort studies, both observing that slower and more variable reaction times at baseline were significantly predictive of all-cause mortality (Shipley et al., 2006; Deary & Der, 2005). In one study reaction time showed stronger predictive validity than that of general intelligence (Deary & Der, 2005). This was the west of Scotland Twenty-07 study in which reaction times at age 56 years were predictive of all-cause mortality risk within a 14-year follow-up (Deary & Der, 2005). The hazard ratios for simple and choice reaction time tasks in predicting mortality (*HR* 1.33 and 1.41) were of similar magnitude to the hazard ratio when general intelligence was the predictor in univariate analysis (*HR* 1.42). However, after adjustment for reaction time the effect of general intelligence was attenuated to non-significance. This led the authors to suggest system integrity as a possible explanation for the intelligence-mortality association, with low-level cognitive function (processing speed) explaining IQ's association with death. The lead author of this article also recently proposed reaction time as a potential biomarker for premature death (Deary, Johnson, et al., 2010, p. 227). One other study has reported on the association between processing speed and mortality risk, using a psychometric rather than experimental cognitive measure. In the Canadian Study of Health and Aging an

inverse association between total performance on four subtests of the Weschler Adult Intelligence Scale (WAIS-R) and mortality risk in adults over 65 years, was due to performance on a single measure, the digit symbol substitution task (Hall, Dubin, Crossley, Holmqvist, & D'Arcy, 2008). The authors reported that a one *SD* decrease in digit symbol score was associated with a 28.6% increase in hazard for mortality after ten years, after adjusting for age, sex and education. Although digit symbol is widely regarded as a psychometric test of processing speed (Deary, Johnson, et al., 2010) it is also said to place high demand on executive function, and it is this cognitive domain that the authors attributed to the association with mortality.

As in the burgeoning literature on associations between psychometric intelligence and behavioural or physical risk factors for morbidity or mortality in longitudinal cohort studies, there is also opportunity to consider cognitive processing speed as a predictor of health outcomes (albeit this may be a more modest exercise given the fewer cohort studies that include experimental processing speed in test batteries). To date, large cohort studies reporting on behavioural and biological correlates of processing speed have largely looked at the associations contemporaneously. For example, the Australian community survey of 7,485 adults in their early twenties, forties and sixties, known as the PATH Through Life Project, reported cross-sectional associations between social and biological markers and reaction time variables. This study found that, besides years in education and age that held the strongest associations with reaction times, greater grip strength, forced expiratory volume, visual acuity, and a lack of diabetes, were most strongly associated with faster and more consistent simple and choice reaction times (Anstey, et al., 2005). In the same study, hypertension, stroke, smoking, and physical activity showed no significant relations with processing speed. Despite the cross-sectional design of this study, the authors interpreted their findings in a specific causal direction; that is, the significant physical markers predicted reaction time performance, rather than vice versa. This directional pathway has emerged from the cognitive ageing literature, as is evidenced from the summary of evidence to date relating inflammatory and haemostatic biomarkers and cognitive processing speed, described in the next section.

Associations between biomarkers and processing speed

The findings from Chapter 5 provide an example of why directions of causation should not be assumed and applied from cross-sectional studies, or even short-term longitudinal studies, given the likelihood of reverse causation. In the present chapter's study, the association between baseline processing speed, and inflammatory and haemostatic biomarkers measured 20 years later, is a first for the literature. All other studies looking at direct relations between these behavioural and biomarker parameters have studied them either contemporaneously, or in the reverse direction; that is, biomarker status predicting later processing speed.

Inflammatory biomarkers

Although studies looking at CRP levels and subsequent global cognitive function or decline report significant findings (for a review see Kuo et al., 2005), associations with follow-up processing speed are less conclusive. For example, in the Longitudinal Aging Study Amsterdam, of 1,284 adults aged 62 to 85 years, no association was observed between CRP and psychometric processing speed after three years' follow-up (Dik et al., 2005). A null finding was also reported from the Edinburgh Artery Study of 452 adults aged on average 62 years: CRP showed no relation to processing speed measured 12 years later with the digit-symbol coding task, although there was a significant association between Interleukin-6 (IL-6) and this psychometric performance task (Rafnsson, Deary, Smith, Whiteman, Rumley, et al., 2007). In cross-sectional studies however higher CRP and related inflammatory biomarkers have been associated with slower processing speeds. In a sample of 88 men and women (average age 57 years) from the Maastricht Aging Study (MAAS), higher CRP related to poorer performance on a Stroop task, a psychometric measure of processing speed – although the association was dependent on age, sex and educational background (Teunissen et al., 2003). In the Sydney Memory and Ageing Study (MAS) of 873 community-dwelling adults aged 70 to 90 years, higher systemic inflammation as measured by interleukin-12 was associated with poorer performance on two psychometric tests of processing speed (Trail Making Test A and Digit-Symbol coding), whereas there was no relation to other cognitive function domains such as executive function and memory (Troller et al., 2011). And in a

Scottish study of over one thousand 70 year-old men and women higher levels of CRP related to poorer performances on three out of four simple and choice reaction time tasks (Luciano et al., 2009). In this study, two out of three of these associations were attenuated to non-significance after adjusting for age-11 cognitive ability, providing the first evidence for reverse causation in inflammation-to-cognition associations.

Haemostatic biomarkers

Perhaps less attention has been given to associations between the haemostatic biomarker fibrinogen and processing speed, although a few studies are worthy of mention. In the Edinburgh Artery Study as described above, high fibrinogen (unlike CRP) was significantly associated with poorer digit-symbol performance after 12 years, although this did not remain significant after adjusting for a contemporaneous measure of premorbid cognitive ability (Rafnsson, Deary, Smith, Whiteman, Rumley, et al., 2007). In the Caerphilly Study of over 1,500 men aged 55 to 69 years, of cross-sectional design, participants in the highest fibrinogen quartile were significantly slower on a choice reaction time task compared to those in the lowest quartile of the haemostatic biomarker (Elwood, Pickering, & Gallacher, 2001). Contemporaneous associations between fibrinogen and four reaction time variables were also reported by authors of the Scottish study as described in the previous paragraph (Luciano et al., 2009). They found that three out of four reaction time performances significantly related to fibrinogen in this older adult sample, and these associations were not explained by premorbid intelligence measured at age 11. A recent meta-analysis of four studies of older adults (including some of the aforementioned) validated the significant association between fibrinogen and processing speed task performance at an aggregate correlation of $r = 0.76$ (Quinn et al., 2011).

The present study

If there is an underlying biology to premorbid cognition-inflammation relations, then an association should be observable between reaction time and

inflammation, if processing speed is the intermediate phenotype between higher-level cognitive reasoning ability and neuronal integrity (Deary, Bastin, et al., 2006), and if ultimately, neuronal integrity is shown to reflect overall bodily integrity. However, it is likely that, even if an underlying determinant exists of the association, lifestyle factors will play an important role in mediating the association between cognition and systemic inflammation over the life course. Using reaction times in place of intelligence test performance, in testing mediation pathways to systemic inflammation, also has an added advantage. Given the strong covariance between IQ and socioeconomic status indicators, statistical overadjustment may occur in models that control for socioeconomic factors. This could give rise to a potential misconception that social factors play a larger role in explaining pathways from premorbid cognition to CVD-related outcomes, than in reality they do. By using reaction time as a measure of cognition, which correlates less with SES than intelligence test scores do, this likelihood of overadjustment is reduced.

This is the first study to report on the association between reaction times and inflammatory biomarkers where the former take temporal precedence. The study makes use of large representative cohorts of adults from the west of Scotland, and the associations can be investigated in three distinct age groups. The aims of the present study are as follows:

1. To investigate associations between baseline measures of cognition—namely simple and choice reaction time (RT) mean and variability—and inflammatory biomarkers 20 years later, in three distinct aged cohorts, with and without adjustment for covariates.
2. To investigate contemporaneous associations between inflammatory biomarkers and reaction time measures, and to test for reverse causation by adjusting for baseline reaction time performances.

Methods

Study population

The study cohorts derive from the west of Scotland Twenty-07 Study, an investigation of individuals assessed longitudinally for twenty years between 1986-7 and 2007 (Benzeval et al., 2009). Three distinct aged cohorts recruited into the study, intended to be approximately 16, 36 or 56 years old at baseline ('wave1'), were assessed another four times at specific time points during two decades (these are known as 'waves2', '3', '4' and '5'). The present study includes data from wave1 and wave5 only. The original purpose of the research was to improve understanding of the determinants of health inequalities in Scotland, exploring socioeconomic indicators, age and demographic characteristics, and physical health indicators. Assessments at baseline (wave1) and follow-up (wave5) involved cognitive testing including reaction time tasks, self-reported and objective physical health measures, and life circumstance questions on occupations and education. General intelligence, using a cognitive test battery, was also measured at both waves in the 1932-born cohort only. At wave5, study participants were invited to consent to give blood for biomarker analysis.

Figure 6.1 gives a flow diagram of the study's sample selection. A total of 4,510 participants were recruited into the study at wave1, including people born around 1932 (N = 1,551), 1952 (N = 1,444), and 1972 (N = 1,515). Twenty years later (wave5) 2,604 had remained in the study that represented 42.7%, 69.2% and 62.2% of the original 1932, 1952, and 1972 birth cohorts. After excluding those who provided proxy or postal-only interviews at wave5, the sample size reduced to 2,568. Blood samples were successfully collected from 2,242 (49.7% of the original wave1 sample).

Measures

Cognitive measures

Simple and four-choice reaction time. A reaction timer was used to measure information processing speed at wave1 and wave5 (see Figure 6.2 for illustration), including simple- and a four-choice-reaction time tasks. The apparatus is described in detail by Deary, Der, and Ford (2001). The simple reaction time task required the participant to press a 'zero' button on the timer box as quickly as possible, when a

zero appeared in a LCD screen positioned at the top left of the box. In the four-choice reaction time task a digit from '1' to '4' appeared in the screen for each trial, and the participant was required to press the correspondingly labelled button as quickly as possible. Eight practice trials preceded a block of 20 simple reaction time trials as well as the block of 40 four-choice reaction time trials. These tests lasted 10 to 15 minutes in total. The stimuli were presented at delays of between one and three seconds after each previous response. Individual's reaction time means and standard deviations were recorded in milliseconds for the simple and 4-choice tasks—based on correct responses only. For the purposes of the present study these four variables are known as: (1) SimpleRT *m*, (2) simpleRT *sd*, (3) choiceRT *m*, (4) choiceRT *sd*. All bivariate correlations among these four at baseline, or at wave5, were positive ($.72 > r > .13$, $p < .05$), and in all but one pairing they were highly statistically significant ($p < .001$). The within-task variables were most highly correlated with one another (simpleRT *m* and *sd,* $.63 > r > .58$; choiceRT *m* and *sd,* $.66 > r > .31$), as were the intra-individual means for simple and choiceRT ($.51 > r > .45$), but less so the intraindividual standard deviations ($.21 > r > .16$). The total number of correct responses was retained, and I used these to exclude individuals with a considerable error rate on choiceRT (>25%).

General cognitive reasoning. At wave1 and wave5 general intelligence was measured—in the 1932 cohort only—using Part 1 of the Alice Heim 4 (AH4) test (Heim, 1970). This is a pencil-and-paper test and was administered to each individual in the study with a researcher present, and timed for ten minutes. In AH4 there are 32 items of verbal reasoning ability assessed by multiple-choice question and 33 items of numeric reasoning presented as short-answer questions, giving a total achievable score of 65. The test shows good reliability (test-retest consistency, $r > .80$) and performance on the various components of the test strongly correlated with a general intelligence factor, $r \geq .80$ (Heim, 1970). In the present study the verbal and numeric reasoning scores were highly correlated ($r > .80$) and therefore I used only the total score for statistical analysis.

Inflammatory biomarkers

Of the 2,568 participants who attended the wave5 interview 2,310 (90%) provided written consent to give blood for the purposes of biomarker analysis (see Figure 6.1). The criteria for non-eligible participants included: Pregnant women, clotting or bleeding disorders, recent mastectomy, and those respondents on renal dialysis. Non-fasting intravenous blood was taken using an arm tourniquet, and up to eight samples each were collected from 2,242 participants. Among these *C-reactive protein* mg/L (CRP) was analysed from a sample collected in a 6mL plain tube (yellow), and *fibrinogen* g/L was analysed from a separate sample collected in a 5mL citrate tube (light blue). These were sent to the Department of Clinical Biochemistry at the Glasgow Royal Infirmary, Glasgow, Scotland for analysis within four days.

I made adjustments to the biomarker data where participants reported use of certain medications. CRP increased by 0.2mg/L if respondents had reported taking statins at wave5 (based on data from Albert, Danielson, Rifai, & Ridker, 2001). Levels of fibrinogen increased by 6% for women reporting use of hormone replacement therapy, based on consistent data reported by De Souza, Stevenson, Davy, Parker Jones, & Seals (1997) and Stefanick et al. (1995). Whereas there is evidence that HRT increases CRP levels by at least 80% (Cushman et al., 1999; Silvestri et al., 2003; Walsh et al, 2000; van Baal et al, 1999), I considered this an extreme adjustment. For example, if, in the 1952 cohort where there was the largest proportion of women taking HRT, CRP data reduced by a factor of 1.8 in cases of HRT-use, the mean level for HRT users would fall significantly below the mean of women not on HRT, $M = 2.3 \pm 0.3$ vs. 4.1 ± 0.3, $t = 4.5$, $p < .001$. Therefore I decided to leave CRP levels unadjusted for HRT, but to use a dummy variable in regression models for women in the 1952 cohort (1 = *HRT use*; 0 = *no HRT*). As so few women in the 1932 and 1972 cohorts used HRT I excluded these cases (n = 3 and 5, respectively). Another drug intervention that may have affected CRP levels is oral contraceptives (Cauci et al., 2008). Again, due to insufficient evidence it was not possible to make a systematic adjustment for this medication. Instead, in the 1972 cohort where 91 participants reported taking oral contraceptives at wave5, I included a dummy variable for its use, in the analysis (1 = *oral contraceptive-use*; 0 = *no oral contraceptives*). This did not affect the 1932 and 1952 cohorts in which no participant reported taking oral contraceptives.

In the 1972, 1952 and 1932 birth cohorts, CRP and fibrinogen at wave5 were strongly correlated (r = .57, .52 and .50 respectively).

Covariates

A range of potential covariates at wave1 and wave5 were tested for their association with baseline cognition, including waist-to-hip ratio (WHR), heart rate, blood pressure, smoking, medication use[3], education, and socioeconomic status variables. Those that were significantly associated ($p < 0.05$) with one or more reaction time variable and the outcome variable—in correlation or between-group tests (see Appendices E and F for effect sizes)—within one or more of the three cohorts[4], were included in the analyses. The following variables measured at baseline and wave5 were included in the models:

Current smoker: dichotomous variable of 'yes' or 'no'.

Resting heart rate (beats per minute): taken manually by a nurse.

Waist-to-hip ratio (WHR): calculated by dividing waist circumference by hip circumference.

Occupational status[5]: the Head of Household's occupational class, coded by the Registrar General Social Class Definition of occupations (1980). Values on this socioeconomic status (SES) variable were reversed, so that high scores were congruous with high status: unskilled = 1, partly skilled = 2, skilled manual = 3, skilled non-manual = 4, intermediate = 5, professional = 6.

The number of years spent in *full-time education*, which was recorded at wave5 only, and which I found to be a significant covariate.

In the 1932 cohort, baseline AH4 scores significantly correlated with the same variables as for reaction times in this cohort. In addition, AH4 scores were significantly lower in aspirin-users versus non-users at wave1 (M = 25.3 ±1.2 vs. 30.9 ±0.6, t = 3.6, $p < .001$), and so I included a dummy variable for *aspirin use* in models where AH4 performance was an independent variable.

[3] Medications included anti-depressants, anti-hypertensives, aspirin, beta-blockers, diabetes medication, SSRIs and statins

[4] For comparison purposes of the results from the three aged cohorts it was decided to include the same covariates in all models, even if covariates were non-significant in models of a particular cohort.

[5] Socioeconomic status indicators measured in the study included occupational level, income, and housing tenure. However, due to strong associations between these three variables and their consistent associations with baseline cognitive performance, I selected the variable which had the least missing data for the analyses, which was occupational status.

Statistical analyses

Exclusion and outlier criteria

ChoiceRT data were excluded from analysis if the errors exceeded 25% (more than ten errors in the 40 trials). This affected seven participants at wave1 and one participant at wave5 from the 1952 birth cohort, two individuals at wave5 from the 1932 cohort, but none among the 1972 cohort. Inflammatory biomarker data were removed from the analysis according to the following exclusion criteria recorded at wave5, which would likely have affected blood status (see Figure 6.1. for numbers excluded):

- Accident or surgery within 31 days
- Blood samples not analysed within four days of being taken
- Participant use of oral corticosteroids
- Participant use of HRT

I identified extreme outliers of biomarker data by inspection of box plots, and excluded these from the analytic models where the biomarker data were continuous. This affected three cases in the 1932 cohort only, where CRP levels were found to be greater than 80mg/L (compared to the next highest value, more than two *SD* lower).

Data transformations

Normal distributions were evident for the majority of variables. Exceptions included CRP and reaction time variables. C-reactive protein showed positive skew in all three cohorts and I therefore log transformed this variable to produce a near-normal distribution. The large majority of reaction time *M* and *SD* data were also positively skewed and so I used their log-transformed values in the second set of analyses, where they were modelled as outcome variables.

AH4 scores were standardised as *Z* scores ($M = 0$, $SD = 1$) to enable a comparison with effect sizes of previous studies, as were reaction time means and standard deviations when they were used as predictor variables in the analysis. As

well as being used as a continuous outcome variable, I recoded CRP as a dichotomous variable, so that *high CRP* was defined as >3mg/L, and values below this were classified as being *normal range CRP*. This threshold has been associated with an increased risk of coronary heart disease in normal adult populations (Pearson et al., 2003). I did not however recode the fibrinogen variable, given the lack of consensus on a clinically relevant threshold.

Statistical models

The analyses are based on cohorts of participants with complete data for: (1) One or more reaction time measure at wave1; (2) One or both inflammatory biomarker measures at wave5; (3) Covariates at both waves as described in the previous section. Tables specify the sample sizes for each set of analysis. Models were run for each age group separately due to different historical and social conditions affecting young, middle- and older-age groups born 20 or 40 years apart.

I used *PASW Statistics 17* to carry out all statistical tests. After conducting exploratory correlation analysis, I investigated associations between cognition and inflammatory biomarkers in the following ways:

1. Multiple linear regressions in which wave1 cognition was modelled to predict a one-unit difference in the inflammatory biomarker at wave5.
2. Logistic regressions to estimate odds ratios based on cognition at wave1 for the risk of high CRP at wave5.

In both sets of analyses, the basic model (Model 1) was adjusted for age only, whereas in subsequent models I adjusted for potentially confounding and mediating variables. For example, Model 2 included significant covariates at baseline that were CVD risk factors, and which may confound cognition-to-biomarker associations, as discussed earlier. In Model 3 I adjusted further for education—a significant correlate of cognition which shows substantial mediation effects in cognitive epidemiological studies. I Model 4 I included CVD risk factors at wave5 to investigate potential mediating effects.

3. In a third and final set of analysis multiple linear regressions modelled contemporaneous associations between cognition and inflammatory biomarkers at wave5, and then the magnitude of attenuation after including baseline cognition, to assess the extent of any potential reverse causation.

In the results of linear regression models, unstandardised beta coefficients are reported with their 95% CI, as well as partial correlations to give an indication of effect size of the association between the cognitive and biomarker variables. To estimate a change in the proportion of variance explained from the basic model to one adjusted for covariates (with equal sample sizes), the squared partial correlations have been used:

$$\text{Partial } r^2_{\text{basic model}} - \text{partial } r^2_{\text{adjusted-model}} / \text{partial } r^2_{\text{basic model}}$$

In logistic regression ORs and 95% CI are reported. Changes in variance explained by odds ratios in adjusted models are calculated as a proportion of the odds ratio from the basic model.

Attrition weight

All models included an inverse-probability weight to control for potential attrition bias at wave5 (M = 2.23, 95th centile = 4.08, maximum value = 19.24). Appendix G describes the methodology involved in computing this weight variable, which was the estimated probability that, among survivors at wave5, a participant completed the wave5 interview and provided a blood sample. It was calculated by S. Seaman at the MRC Biostatistics Unit in Cambridge UK, using logistic regression with several covariates that included, but were not limited to, sex, cognitive ability, socioeconomic status, health indices, and smoking. I decided it was unnecessary to truncate these weights, given that the maximum value was less than 20 times the average weight, ensuring stability of estimates from the final analyses (Seaman and White, 2011).

Results

Table 6.1 compares baseline characteristics of the 1932, 1952, and 1972 analytic cohorts with their respective groups of participants who reached wave5 but were excluded from the analysis. No statistically significant differences were observed between excluded and study participants on any of the baseline measures that included cognition, cardiovascular risk factors and socioeconomic indicators. However, a significantly lower proportion of women from the 1972 cohort were observed in the analytic cohort (χ^2 = 4.49, p = 0.034), due to the exclusion of pregnant women from the blood collection.

Table 6.1 also allows a comparison of the present study's three age groups according to baseline characteristics. Although this is not a principal issue of the study's hypotheses, a descriptive comparison is helpful in the interpretation of any age-specific findings. In the three analytic cohorts baseline reaction times were fastest on average in the 1972 cohort, and slowest on average in the 1932 cohort. The oldest aged sample also showed greater variability on simple and choiceRT tasks, and the 1952 cohort were least variable on choiceRT but equal to the younger sample on simpleRT sd. WHR was highest in the middle age group, and lowest in the younger group. The greatest proportion of smokers at baseline was among the 1952 cohort (42%), followed closely by the 1932 cohort (34%). As expected the 1972 cohort were infrequent smokers (17%) at age 16 years. As expected from educational policy changes in Scotland, 1972 cohort had spent the most time in education (M = 13.9 years) and the 1932 cohort were the earliest school-leavers (M = 10.6 years).

Baseline cognition and twenty-year later inflammation

Several interaction effects were observed in basic models between sex and RT variables at wave1 in predicting inflammatory status at wave5 (Appendix H lists these significant interactions). These were tested due to the reported sex differences in reaction time performance and inflammatory biomarkers. I therefore decided to run the models separately for men and women. Table 6.2 includes descriptive characteristics of men and women for each of the three cohorts, and reports any statistically significant sex differences ($p < .05$). Women aged 36 and 56 years (1932 and 1952 cohorts at wave1, and 1952 and 1972 cohorts at wave5) showed

significantly less consistency on choiceRT at baseline compared to men. There were no other sex differences on reaction time variables, apart from women of the 1952 cohort showing slower baseline simpleRT than men. Sex differences were also observed on inflammatory biomarker levels at wave5. On average women of the 1952 and 1972 cohorts were significantly higher on CRP and fibrinogen than men. An equal proportion of men and women smoked within each of the three cohorts, although more men than women were smokers at wave5 among the 1972 cohort. WHR was lower among women than men across all cohorts, and this is to be expected. Heart rate was generally higher among women. Men and women spent an equivalent time in education, within each of the three cohorts.

Tables 6.3 and 6.4 report unstandardised beta coefficients for the prediction of CRP and fibrinogen according to baseline RT variables, for men and women respectively.

1972 cohort

In the youngest men, performance on two out of four reaction time measures was associated with CRP status at follow-up. That is, in a basic age-adjusted model faster and more consistent choiceRT at age 16 years significantly predicted lower CRP levels at age 36 years (partial r = .13 and .17). A one *SD* advantage in choiceRT *m* and *sd* were associated with decreases of 1.14 mg/L and 1.18 mg/L CRP respectively (values are antilog transformed). These effects were largely attenuated when adjusting for baseline covariates that included smoking and occupational status (by 77.9% and 60.8% respectively; individual attenuation effects by smoking and SES were equivalent) and were no longer statistically significant (partial r = .06 and .11), and some further attenuation was observed in the fully adjusted models (partial r = .04 and .08). In women of the 1972 cohort, one out of the four reaction time measures was related to CRP in the basic model. A one *SD* reduction in simpleRT variability at wave1 was associated with a reduction of 1.24 mg/L CRP at wave5 (partial r = .18, $p < .001$). This effect size attenuated by 23.9% in the fully adjusted model (Model 4) and remained statistically significant (partial r = .14, $p < .005$). There were no significant associations between reaction time variables and fibrinogen in the 1972 cohorts.

1952 cohort

In three-quarters of models associations between baseline RT performances and CRP status at wave5 were in the expected direction but non-significant; that is, faster and more consistent reaction times related to lower CRP in men and in women born around 1952. Faster and more consistent RT was significantly associated with lower levels of fibrinogen in men, in three out of four models, simpleRT *m* (partial $r = .15$, $p = 0.004$), choiceRT *m* (partial $r = .12$, $p < .030$), and simpleRT *sd* (partial $r = .12$, $p = .027$). The effect of simpleRT speed on fibrinogen attenuated by 17.5% in a fully adjusted model, and remained statistically significant (partial $r = .14$, $p = 0.010$). The effects of choiceRT *m* and simpleRT *sd* on fibrinogen, were attenuated to non-significance (45.3% and 35.7% reductions) in models that adjusted for baseline CVD risk factors, including smoking, occupational status and heart rate. Among women, reaction time performances at baseline bore no relation to fibrinogen status twenty years later.

1932 cohort

No significant associations were observed among men and women in the 1932 cohort between baseline reaction times and wave5 CRP, with one exception. In men, more consistent choiceRT was significantly associated with higher CRP at follow-up (partial $r = -.17$, $p = .017$). This effect increased slightly in magnitude in adjusted models, and by 50% in the fully adjusted model (partial $r = -.21$, $p = .004$). Similarly, there was no relation between RT and fibrinogen in this oldest cohort, with one exception, again in the unexpected direction and in men. Faster simpleRT was associated with higher fibrinogen after 20 years (partial $r = -.17$, $p = .020$). Adjustment for baseline and wave5 covariates increased the magnitude of effect (model4) by approximately one third (partial $r = -.19$, $p = .009$).

In the 1932 cohort higher AH4 scores at baseline were associated with higher CRP levels twenty years later among men (coefficient = -.079, 95% CI = -.136 to -.022, partial $r = -.193$, $p = .007$, $n = 198$). However, this association largely attenuated (82.3%) after adjustment for baseline covariates that included smoking status, occupation, WHR, and aspirin use (-.040, 95% CI -.110 to .031, partial $r =$ -

.080, p = .268). There was no association among women (-.011, 95% CI -.157 to .035, p = .652, n = 267). There were no statistically significant associations between baseline AH4 scores and fibrinogen at wave5 in men (-.083, 95% CI -.198 to .033, p = .160, n = 192) or women (-.035, 95% CI -.052 to .121, p = .429, n = 257).

Cognition and elevated C-reactive protein

The proportions of men and women with high CRP at wave5 were 21.6% and 35.2% in the 1972 cohort, 32.8% and 40.6% in the 1952 cohort, and 40.3% and 39.9% in the 1932 cohort (see Table 6.2). The greater proportion of women than men with high CRP in the 1972 and 1952 cohorts reached statistical significance. Interaction effects were observed in logistic regression models that predicted high CRP, between sex and several reaction time variables, in the 1972 and 1932 cohorts (see Appendix H for list of significant interactions). Therefore, odds ratios are reported for men and women separately in all cohorts.

Tables 6.5 and 6.6 show odds ratios for baseline RT predicting high CRP, for men and women respectively. The RT variable data used in these models were inverted so that better reaction time performances (faster and less variable) were reflected in higher scores.

1972 cohort

In the 1972 male cohort, performances on three out of four RT tasks were related to the reduced risk of high CRP at wave5. That is, faster choiceRT and more consistent simple and choiceRT at baseline were significantly associated with the reduced risk of high circulating CRP twenty years later (*OR* 0.71 to 0.79, $p < .01$). These effect sizes were attenuated after adjusting for baseline smoking and occupational status, by between 48% and 68%, and although these remained inverse associations in all adjusted models, they were no longer statistically significant. Among females of the 1972 cohort, one out of four reaction time variables was predictive of CRP status at follow-up; simpleRT *sd* was significantly associated with the reduced odds of high CRP status (*OR* 0.69, 95% CI 0.58 to 0.83), which

attenuated by only 6% in the fully adjusted model and the effect remained statistically significant (*OR* 0.71, 95% CI 0.56 to 0.96).

1952 cohort

In men of the 1952 cohort, inverse associations were observed between three out of four RT variables and risk of high CRP, although none was statistically significant. In women, two out of four of the basic models were statistically significant. Faster simple and choiceRT predicted the reduced risk of high CRP after twenty years (*OR* 0.85, 95% CI 0.72 to 0.99, and *OR* 0.82, 95% CI 0.70 to 0.97, respectively). These effect sizes were reduced by 40% and 72% respectively after adjustment for baseline covariates, and were no longer statistically significant.

1932 cohort

Reaction times did not predict high CRP in men and women of the 1932 cohort, with one exception. In men, more variable choiceRT related to the increased odds of high CRP (*OR* 2.01, 95% CI .47 to 2.74, $p < .001$). The magnitude of this effect remained constant in the fully adjusted model.

Higher AH4 scores at wave1 were related to the reduced odds of high CRP at wave5, a highly statistically significant effect in men (*OR* 0.66, 95% CI 0.52 to 0.83, $p < .001$), and close to significant in women (*OR* 0.84, 95% CI 0.70 to 1.01, $p = .068$). After controlling for baseline CVD covariates the effect in men was no longer statistically significant (*OR* 0.81, 95% CI 0.61 to 1.06, $p = .122$).

Cognition-to-inflammation: Reverse causation?

Table 6.7 presents correlation coefficients for the associations between reaction time variables at wave5 with respective performance scores at baseline, by sex. The large majority of the positive associations were highly statistically significant ($p < .001$). Across all three cohorts, choiceRT *m* showed greatest stability over 20 years ($r = .37$ to 62), and simpleRT *m* and choiceRT *sd* showed a similar range of stability coefficients ($r = .25$ to 44 and $r = .28$ to 40 respectively), with the

exception of choiceRT *sd* among 1932 cohort males (r = .16). SimpleRT *sd* was consistently the least stable over 20 years (r = .09 to .27). The 1952 cohort, where reaction times at age 36 and 56 years were correlated, showed the highest coefficients, whilst the 1932 cohort (56 and 76 years) showed the weakest correlations.

Next, linear regression models were run where this time the biomarkers were independent variables, and wave5 reaction times were the outcome variables. I then tested for reverse causation by adjusting for baseline reaction times. There were no interaction effects between sex and inflammatory biomarkers, according to linear regression models predicting wave5 reaction times, with one exception. In the 1952 cohort sex interacted with CRP to predict choiceRT *sd* (-.153, 95% CI -.099 to -.011, p = .014). However, the direction of association between CRP and choiceRT *sd* was similar for men and women (see Appendix H), and therefore regression models were run for the total cohorts, rather than dividing by sex group as in the previous analyses.

Table 6.8 presents the beta coefficients for associations between contemporaneous RT and inflammatory status, with and without adjustment for baseline RT. There were no significant cross-sectional associations between CRP and fibrinogen and reaction times in the 1972 and 1932 birth cohorts. However, in the 1952 cohort at wave5 higher CRP levels were associated with three out of four of the RT measures, slower simpleRT (partial r = .11, p = .002) and choiceRT (partial r = .13, p < .001), and more variable choiceRT (partial r = .15, p < .001). These associations were not explained by reverse causation; that is, after adjustment for RT performance at wave1, effect sizes increased either by 15.1% at most or were attenuated by 17.5% at most, and the contemporaneous associations remained statistically significant. In this cohort, higher fibrinogen was also associated with the same three reaction time performances, slower simpleRT (partial r = .08, p = .020) and choiceRT (partial r = .07, p = .045), and more variable choiceRT (partial r = .099, p = .006). After adjustment for baseline RT the association between choiceRT *m* and fibrinogen attenuated to non-significance (reduction of 47.8%). Reverse causation explained less of the associations between simpleRT *m,* and choiceRT *sd* and fibrinogen respectively, and these models attenuated by only 9.4% and 11.8%.

In the 1932 cohort (n = 419) higher AH4 scores at wave5 were significantly associated with lower CRP (regression coefficient = -3.21, 95% CI -5.84 to -0.58,

partial r = -.115, p = .017). This effect fully attenuated after adjustment for baseline AH4 performance (0.19, 95% CI -1.34 to 1.72, partial r = .012, p = .806). I found no association between wave5 fibrinogen and contemporaneous AH4 performance (0.25, 95% CI -1.18 to 1.69, partial r = .017, p = .730).

Discussion

The present longitudinal cohort study is the first to investigate the direction and strength of association between baseline cognitive processing speed, and inflammatory and haemostatic status at long-term follow-up. Using three specific age groups in adulthood from a representative regional sample, the results may be used to make inferences about the nature of these associations throughout the life course, in the general population. The testing of reverse causation in the contemporaneous associations at wave5 of the study provides supplementary data for further informing this issue.

As hypothesised, faster and less variable baseline reaction times were associated with reduced CRP status after 20 years, albeit significant results were restricted to the youngest cohort and effect sizes were small—congruent with the existing literature. Furthermore, the adjustment of baseline covariates reduced the effects to non-significance among men. In women of the 1972 cohort, for whom only simpleRT variability related to CRP, the effect remained statistically significant in fully adjusted models. The relation of faster and more consistent baseline processing speed to lower fibrinogen after twenty years was significant among 1952 cohort males only, and the relation with simpleRT speed was independent of CVD covariates, education, and socioeconomic status. The contemporaneous associations between faster and less variable simple and choiceRT and the inflammatory and haemostatic biomarkers observed in the 1952 cohort were independent of reaction time performances from twenty years past. In the 1932 cohort where there was additional information on cognitive function, with baseline scores from a psychometric intelligence test, reverse causation fully accounted for the inverse association between the AH4 ability score and CRP measured contemporaneously at age 76 years. That is, after controlling for the cognitive ability score from age 56 years, the significant association 20 years later was no longer significant.

Choice reaction time predicts CRP 20 years later in young men

The effect sizes in the present study's 1972 male cohort, of a one *SD* change in the choiceRT variables in association with a unit change in CRP (partial r = .13 for speed and r = .17 for variability), equate to the direction and magnitude of associations from two previous longitudinal cohort studies reporting a one *SD* increase in baseline psychometric intelligence scores in relation to a unit reduction in the follow-up inflammatory biomarker. The first is the NCDS study, as reported in the previous chapter, which found a significant inverse association between age 11 cognitive ability and CRP status after 34 years, with a partial r of .13 (see also Calvin, Batty, Lowe, & Deary, 2011). The second, the Vietnam Experience Study, reported an inverse association between intelligence test scores at age twenty years and erythrocyte sedimentation rate—a stable inflammatory biomarker—nearly twenty years later in men, of the magnitude partial r = .20 (Phillips et al., 2011).

Unlike in the present study however, the cognition-to-inflammatory biomarker associations in these two previous studies retained statistical significance in fully adjusted models. This is quite likely due to the increased statistical power from their larger sample sizes, because the magnitude of the effect sizes (partial correlations) across studies is similar from equivalent models accounting for multiple covariates. For example, in the present study partial correlations for the effects of choiceRT speed and variability on CRP, in fully adjusted models, were partial r = .04 and .08 respectively. The equivalent effect sizes in the two aforementioned studies where intelligence test scores were the predictor were partial r = .04 and .07 respectively (Calvin, Batty, Lowe, et al., 2011; Phillips et al., 2011).

Sex differential effects

The effect sizes for choiceRT on CRP in males were not seen among females of the 1972 cohort. However, in women less variable simpleRT predicted lower CRP twenty years later (partial r = .22). This effect remained statistically significant after accounting for all potential covariates, and in the logistic model a one *SD* advantage

in simpleRT predicted a 26% reduced odds of elevated CRP. The strength of association from this predictor is perhaps surprising, given the low stability of simpleRT *sd* compared to that of the other three reaction time variables in Twenty-07 (see Deary & Der, 2005, and the correlation coefficients reported in this chapter). There may be systematic differences between men and women in response to the simpleRT task that may yet explain the effect. In older adult cohorts at least, women compared to men are more variable but also more accurate on reaction time tasks (Der & Deary, 2006; Reimers & Maylor, 2006). However, in the 1972 cohort there were no sex differences in any of the RT variables, which might have led to insights in to this finding.

Mediation by smoking

An explanation as to why reaction times predicted CRP in men but not women might be interpreted from the observed attenuation effects in linear and logistic models after adjustment for smoking—at baseline (Model 2) and again at wave5 (Model 4). Although smoking prevalence was similar for men and women, the effects of smoking on inflammatory status may not have been. In a longitudinal cohort study of 2,590 adults aged 30 to 89 years, smoking among men predicted more than double the risk of elevated CRP levels after four years, but there was no effect of smoking on CRP among women (Onat, Can, & Hergenç, 2008). This implies that cigarette smoking could explain a substantive degree of the association between processing speed and CRP in the present study. Whether smoking is a confounder of the association, or mediates the effect, is another matter. However, several reasons would suggest that it is more likely to be a mediating variable in the context of the present study. If smoking was a confounder it would need to have a causal effect on processing speed as well as CRP. However, the 1972 cohort were just 16 years' old at baseline, and therefore would be unlikely to have smoked for a significant period before wave1 for it to have had adverse impact on processing speed. Furthermore, evidence from meta-analysis of eleven randomized controlled trials suggests that smoking has a short-term advantage for reaction times (Heishman, Kleykamp, & Singleton, 2010). That there is much greater evidence for the reverse direction of association, that lower cognitive reasoning ability predicts

the increased likelihood of smoking in subsequent years (Batty, Deary, & Macintyre, 2007b; Batty, Deary, Schoon, & Gale, 2007c; Taylor et al., 2003), leads to the inference that smoking might be a mediator in the models.

Cohort-specific effects

ChoiceRT performance starts to slow from early adulthood, and increases in variability in one's 30s (Der & Deary, 2006). Therefore the choiceRT measures in the study's 1972 cohort may better reflect optimal performance than the older cohorts—or at least they may be more reliable proxies for 'premorbid' neurological integrity. This means that using the 1972 cohort to test causal pathways from processing speed to inflammation has the greatest validity among the three age-specific cohorts. The lower effect sizes and frequent null associations from the results of 36 and 56 year-olds at baseline may therefore be due to age-specific effects and/or comorbidities, thus their departure from best-ever (the most 'system integrity'-indicative) cognitive function. Nevertheless, in logistic regression faster simpleRT and choiceRT were still significantly protective from elevated CRP status among women in the 1952 cohort, reducing the odds by 15% and 18% respectively.

Reverse findings in older adults

An unexpected finding was from the oldest cohort—those who were 56 years at baseline and 76 at follow-up—where two significant effects were observed in men in the opposite direction to what I expected. In a linear model more consistent choiceRT predicted higher CRP, and in a logistic model more consistent simpleRT related to an increased risk of high CRP status. Both of these effects were statistically significant in the fully adjusted models. I noted a similar effect with simpleRT *m* and fibrinogen in the oldest men too. That these should be real effects with biological plausibility is questionable, and several alternative explanations must first be ruled out.

The first possibility refers to sampling and survival bias. Despite the inclusion of attrition weighting in all analytic models, the 1932 cohort lost the greatest proportion of its original sample to mortality (over a third), and so there may

be factors specific to survival, and participant compliance, that caused the effect. For example, it is possible that a subgroup of the original sample with high cognitive ability in their fifties who developed high risk CVD profiles, survived longer than peers who also carried a high CVD-risk profile but whose cognitive performance was slower and more variable at the same age; therefore a disproportionately higher number of these male participants were retained in the study. If this was the case however, I might have expected higher functioning adults to be successfully managing their health problems with increased medication use, but I found no evidence that baseline cognitive function predicted prescription drug-use at wave5.

Second, a related issue concerns the study sample, selected from a region in the UK with the highest recorded mortality rate since the 1950s (McCartney, Collins, Walsh, & Batty, 2011). This phenomenon is a complex social and public health issue known as the Glasgow effect. In the Twenty-07 study where the age at wave5 of the 1932 cohort was beyond the average life expectancy for many areas within this region, survivors are exceptional and therefore results of the older cohort may not be generalisable to the Scottish nation or UK as a whole. In support of this is that mean fibrinogen levels in the three aged cohorts were higher than pooled data from 31 population-based cohort studies (The Fibrinogen Studies Collaboration, 2007).

Third, the unexpected findings may also be due to the inconsistent performance of biomarkers in older populations. Specifically, CRP and fibrinogen in older age groups versus middle-age adults may have less predictive validity for CVD outcomes or related-mortality (Kritchevsky, Cesari, & Pahor, 2005), although less is known about how these biomarkers perform in older age due to the relatively fewer studies. If the variables themselves are to be viewed as unreliable for the oldest cohort in this study, then the results for this group are implausible. Finally, the unexpected results may have arisen by chance, particularly given the number of tests. The issue of multiple testing is discussed further down.

RT associations with fibrinogen in mid-adulthood

I observed another specific age-cohort effect in models predicting fibrinogen. The association between reaction time measures and this biomarker were significant only for men of the 1952 cohort. Given that better performance on three out of four

reaction time variables were significantly predictive of lower fibrinogen levels twenty years later (partial r = .12 to .15), is evidence that these effects are due to more than chance alone. CRP and fibrinogen levels increase at the same rate throughout the life course (Ferrucci et al., 2005), and so it is unlikely that their unique age-trajectories are responsible for reaction times relating specifically to CRP in young adulthood and to fibrinogen in mid-adulthood. Instead it is possible that more than one mechanistic pathway may account for the role of cognition in predicting health outcomes.

An alternative explanation is that smoking again plays a mediating role in the associations between reaction time and fibrinogen in 1952 men. In a review of 31 international prospective cohort studies, the effect of smoking on fibrinogen levels in men was reported to be twice that of women (The Fibrinogen Studies Collaboration, 2007). Indeed after adjustment for baseline smoking and occupational status in two out of the three significant basic models, the predictive effects of processing speed on fibrinogen were non-significant, and further attenuation effects were seen after adjustment for smoking status (along with other covariates) at wave5. The exception was that simpleRT speed at age 36 continued to significantly predict fibrinogen at age 56 in men, in the fully adjusted model, leaving open the possibility of potential mechanisms beyond the physical effects of smoking. If cigarette use is a strong mediator in pathways linking processing speed to fibrinogen, then it is not clear why I did not observe its effect in the younger cohort, unless the adverse effects of smoking on CRP levels occur at a faster rate to those affecting fibrinogen.

Is there potential for system integrity?

The potential for system integrity to in part explain significant associations between higher-level cognitive function and inflammation and haemostasis, remains plausible given that this study's results show similar effect sizes with arguably lower-level cognitive tasks than intelligence tests. As discussed, reaction times and psychometric intelligence are strongly correlated, and their association highly heritable (Luciano et al., 2001). ChoiceRT measures were more predictive than equivalent simpleRT measures, and given that this more demanding processing speed task also more strongly relates to neurological measures of white matter

integrity (Penke et al., 2010), is further support for system integrity theory, albeit these data are only so far available for older adult cohorts. Faster choiceRT is also more strongly predictive of low-risk mortality than simpleRT (Deary & Der, 2005), and as is also clear, it is a more stable performance variable. It should therefore be the focus of continued research in this field.

However, the sensitivity of both behavioural and biomarker measures to lifetime insults (from ill-health or adverse health behaviours) and normal ageing processes, makes testing a system integrity hypothesis problematic. This is particularly the case in older adult groups, and in the present study's 1932-born cohort. Furthermore, appreciating the underlying cause of the association between cognition and inflammation, and potential direction of causation, is limited in the present study by the absence of baseline biomarker status. Testing the contemporaneous relationships between processing speed and CVD biomarker, for reverse causation, is still an effective way of informing this issue however. That better performance on three out of four reaction time variables at age 56 related to lower CRP and fibrinogen at the same age, and that the majority of these associations were not explained by reaction time performances 20 years earlier, tells us a few things: (1) System integrity cannot fully explain the nature of these associations, and which is clear from the evidence above; (2) It is not only underlying cognitive function that drives the association between processing speed and these biomarkers in later life.

Given the substantial attenuation effects observed in covariate-adjusted models, and particularly the likely mediating role of smoking in the younger cohort, it is proposed that a behavioural lifestyle model explains a greater proportion of the effect in cognition-to-biomarker pathways than system integrity. On the other hand, some effects retained statistical significance even after adjusting for socioeconomic status, education, and CVD risk factors. This suggests that it may be premature to reject the system integrity hypothesis in explaining relations between cognitive processing and systemic inflammation.

Strengths

It is novel for a large population cohort study to have the combination of behavioural processing speed measures and biomarker data (and separated by an extensive follow-up period) such as in the Twenty-07 cohort, and this is a main strength of the present study. It is the first investigation to assess cognitive processing speed as a predictor of inflammatory and haemostatic status after longitudinal follow-up, thus contributing to a body of literature that has depended upon psychometric intelligence test scores as the principal measure of cognitive function. As IQ-type test performance can be influenced by educational and social contexts, reaction time as a measure of premorbid cognitive function may be less confounded by socioeconomic factors, albeit it is more sensitive to ageing effects. Second, the present study included these data points for three distinct age groups in youth and adulthood. This allows inferences to be made about the generalization of cognition-biomarker associations over the life course, and as perhaps illustrated above this is a dynamic and shifting relationship. More important, the inclusion of the younger cohort means that reaction time performance is measured at a premorbid phase before ageing effects adversely affect optimal processing speed. In contrast, in the 1932-born cohort the effects of ageing are being detected more than etiological processes. To illustrate this point, I observed in the oldest cohort for which AH4 test scores were available, stable psychometric intelligence at age 56 entirely accounting for the contemporaneous association between CRP and the AH4 score at age 76, whereas reaction times that are more sensitive to ageing processes did not show such reverse causation, at least for those significant contemporaneous associations in the 1952 cohort.

Limitations

There are limitations to the present study that must be discussed here.

First, although the Twenty-07 study was intended as a representative sample of adults living in the west of Scotland region, and sample sizes are large, the oldest cohort especially may not be representative of similarly aged cohorts from other UK regions, given the increased health problems associated with this area of Scotland. Therefore the results derived from adults born in 1932 may not be generalisable to the broader background population.

Second, in any longitudinal study where the baseline occurs in adulthood, there is always the issue of confounding by influences occurring prior to the study. For example, full-time education in these older samples would have been completed prior to the study onset, and could have driven the associations between cognition and inflammation; educational achievement is related to increased inflammatory status in adult life (Gimeno, Ferrie, et al., 2008), although any effect of education on processing speed is as yet unknown. Although I attempted to overcome the issue of overadjustment for education, by using a cognitive variable with less cultural bias, the cost of using RT in adulthood was that it may have been more susceptible to confounding in the older cohorts. This means that results from the youngest cohort are at lowest risk of confounding, and ultimately more reliable.

Third, I conducted multiple testing which may have incurred, in particular, type 1 error, and therefore the results are interpreted with caution. For example, in basic models an association between two or more reaction time variables with the biomarker outcome was given greater importance, than associations that were simply held with one out of four reaction time performance levels.

Finally, the study would have benefited not only from a measure of biomarker status at baseline (emerging studies that include blood sampling will enlighten this issue), but it would have also been informative to include additional biomarkers each of inflammation and haemostasis. Replication studies of this area would certainly be strengthened by the inclusion of multiple markers. For example, interleukin-6 is viewed as a more reliable biomarker of habitual inflammatory status, and is a more robust predictor of CVD, cancers and diabetes, compared to CRP (for a review see Singh & Newman, 2011).

Conclusion

Just as premorbid psychometric intelligence has predicted a range of CVD outcomes in longitudinal studies—including emerging risk markers—cognitive processing speed operationalised using simple and choice reaction times and intraindividual variances, are also predictive when measured in youth. Given the possible closer affinity to neuronal integrity of low-level processing speed – versus general intelligence – this study's findings could lend greater validity to system

integrity theory. However, this explanation is made less compelling in the current findings by evidence that smoking may be a strong mediator of the association. An advantage in choice reaction time performance may underlie the development of higher reasoning capability, which ultimately leads to the decision to not take up smoking or to quit, in more cases than not. Such pathways can be tested more formally if cohort studies choose to test on a range of cognitive variables over time.

Table 6.1 Baseline characteristics of included and excluded participants: Twenty-07.

	1972 cohort					1952 cohort					1932 cohort				
	Included		Excluded			Included		Excluded			Included		Excluded		
N	759		183		*p*[a]	843		156		*p*	528		135		*p*
Female, *N* (%)	404	(53.2)	114	(62.3)	*.03*	458	(54.3)	84	(53.8)	*.56*	298	(56.4)	86	(63.7)	*.24*
Cognitive measures															
SimpleRT m	291.6	*56.5*	299.8	*80.3*	*.50*	309.4	*74.6*	301.9	*72.1*	*.21*	340.4	108.8	347.2	*126.5*	*.76*
SimpleRT sd	71.9	*47.5*	76.8	*61.7*	*.60*	65.2	*41.7*	62.0	*38.5*	*.73*	84.5	60.2	92.8	*68.7*	*.70*
ChoiceRT m	567.1	*69.3*	568.2	*72.4*	*.41*	615.4	*80.9*	609.8	*89.0*	*40*	704.0	105.3	708.0	*111.4*	*.97*
ChoiceRT sd	111.1	*32.1*	109.0	*31.5*	*.42*	112.2	*29.5*	110.3	*29.4*	*.26*	127.7	33.6	127.9	*32.7*	*.83*
AH4											30.2	11.6	28.7	*10.6*	*.33*
Covariates															
Smoker, *N* (%)	125	*16.5*	26	*14.2*	*.87*	349	*41.4*	80	*51.3*	*.19*	179	33.9	53	*39.3*	*.61*
WHR	0.85	*0.07*	0.87	*0.10*	*.85*	0.88	*0.09*	0.89	*0.09*	*.46*	0.86	0.08	0.86	*0.08*	*.56*

	1972 cohort					1952 cohort					1932 cohort				
	Included		Excluded			Included		Excluded			Included		Excluded		
N	759		183		*p*[a]	843		156		*p*	528		135		*p*
Heart rate	72.9	*10.0*	73.1	*10.6*	*.41*	70.9	*9.8*	72.5	*11.0*	*.08*	71.2	9.1	72.9	*9.6*	*.20*
Education	13.9	*3.1*	13.7	*2.8*	*.35*	12.7	*3.2*	12.6	*3.3*	*.99*	10.6	2.8	10.5	*2.3*	*.62*
Occupational status, *N* (%)					*.79*					*.46*					*.63*
Unskilled	14	(1.9)	6	(3.3)		20	(2.4)	5	(3.2)		25	(4.8)	3	(2.2)	
Partly skilled	94	(12.6)	14	(7.7)		87	(10.5)	13	(8.2)		66	(12.6)	12	(8.7)	
Skilled manual	159	(21.2)	40	(22.0)		145	(17.4)	34	(21.5)		92	(17.5)	29	(21.0)	
Skill non-manual	184	(24.6)	47	(25.8)		188	(22.6)	34	(21.5)		133	(25.3)	46	(33.3)	
Intermediate	218	(29.1)	60	(33.0)		282	(33.9)	59	(37.3)		165	(31.4)	39	(28.3)	
Professional	80	(10.7)	15	(8.2)		110	(13.2)	13	(8.2)		44	(8.4)	9	(6.5)	

Note. Values are means and *standard deviations*, except for categorical variables where the group size (and percentage) are shown. Sample sizes vary according to missing data on each variable.
[a] Independent samples *t*-tests compared included versus excluded groups, with the exception of sex and smoking group differences which were based on chi-square. No statistically significant group differences except for distribution of sexes in 1972 cohort.

Table 6.2 Cohort characteristics by sex group: Twenty-07.

	1972 cohort					1952 cohort					1932 cohort				
	Men n = 355		Women N = 404			Men N = 383		Women N = 460			Men N = 229		Women N = 299		
	M	*SD*	*M*	*SD*	*p*[a]	*M*	*SD*	*M*	*SD*	*p*	*M*	*SD*	*M*	*SD*	*p*
Wave1 cognition															
SimpleRT m	289.3	*56.7*	293.4	*56.3*	.322	302.0	*68.3*	315.8	*79.2*	.005	347.8	*114.4*	336.2	*105.2*	.237
SimpleRT sd	75.5	*53.6*	68.6	*41.2*	.054	62.9	*35.8*	66.9	*45.8*	.236	84.1	*60.2*	85.9	*62.1*	.716
ChoiceRT m	566.9	*69.0*	566.9	*69.8*	1.00	614.8	*79.0*	616.2	*82.4*	.821	711.7	*94.9*	698.2	*112.2*	.080
ChoiceRT sd	109.9	*30.9*	112.1	*33.1*	.359	107.6	*28.2*	116.0	*30.0*	< .001	119.4	*30.8*	133.9	*34.4*	< .001
Wave1 covariates															
Smoker, *N* (%)	59	(16.6)	66	(16.3)	.916	174	(45.8)	180	(39.2)	.055	87	(38.0)	93	(31.1)	.098
WHR	0.90	*0.06*	0.81	*0.05*	< .001	0.96	*0.06*	0.81	*0.05*	< .001	0.93	*0.05*	0.81	*0.05*	< .001
Heart rate	70.7	*10.2*	74.8	*9.4*	< .001	69.4	*10.2*	72.1	*9.3*	< .001	70.9	*8.8*	71.4	*9.3*	.591
Occupational status, *N* (%)															
Unskilled	6	(1.7)	8	(2.0)	.496	11	(2.9)	9	(2.0)	.005	8	(3.5)	17	(5.7)	.039
Partly skilled	37	(10.5)	57	(14.3)		31	(8.2)	57	(12.4)		26	(11.4)	40	(13.4)	
Skilled manual	83	(23.6)	76	(19.0)		79	(20.8)	67	(14.6)		50	(21.8)	43	(14.4)	
Skill non-manual	83	(23.6)	101	(25.3)		70	(18.5)	119	(26.0)		46	(20.1)	88	(29.4)	
Intermediate	103	(29.3)	116	(29.1)		129	(34.0)	154	(33.6)		79	(34.5)	86	(28.8)	
Professional	39	(11.1)	41	(10.3)		59	(15.6)	52	(11.4)		20	(8.7)	25	(8.4)	
Wave5 outcomes															

CRP	2.33	*3.02*	3.67	*5.17*	< .001	3.28	*4.12*	4.50	*7.12*	.021	4.77	*6.84*	4.70	*5.52*	.399
High CRP, *N* (%)	76	(21.6)	141	(35.2)	< .001	125	(32.8)	185	(40.6)	.021	91	(40.3)	116	(39.9)	.085
Fibrinogen	3.19	*0.57*	3.41	*0.73*	< .001	3.48	*0.67*	3.62	*0.71*	.004	3.65	*0.77*	3.81	*0.72*	*.021*
Metabolic syndrome, *N* (%)	90	(25.6)	64	(16.0)	.001	152	(40.6)	156	(35.1)	.100	66	(29.5)	142	(47.8)	.014
Wave5 cognition															
SimpleRT m	275.1	*53.1*	275.1	*50.5*	.987	298.1	*74.8*	301.8	*76.2*	.370	361.9	*187.6*	370.6	*151.3*	.188
SimpleRT sd	49.6	*36.4*	52.3	*34.1*	.307	73.4	*121.3*	76.3	*154.2*	.184	126.8	*267.6*	138.7	*277.1*	.135
ChoiceRT m	533.3	*69.7*	537.9	*62.3*	.343	633.8	*89.7*	637.2	*99.7*	.634	801.5	*216.2*	805.1	*176.7*	.697
ChoiceRT sd	86.4	*24.9*	96.0	*26.1*	< .001	115.6	*50.5*	130.9	*85.3*	< .001	185.9	*213.5*	202.0	*262.1*	.118
Wave5 covariates															
Education	13.9	*3.3*	14.0	*3.0*	.889	12.9	*3.4*	12.5	*2.9*	.060	10.5	*3.0*	10.7	*2.7*	.486
Smoker, *N* (%)	112	(31.7)	93	(23.0)	.007	90	(23.5)	125	(27.2)	.216	14	(18.1)	43	(14.4)	.254
WHR	0.92	*0.06*	0.83	*0.07*	< .001	0.96	*0.06*	0.85	*0.07*	< .001	0.96	*0.06*	0.87	*0.07*	< .001
Heart rate	64.6	*10.6*	67.0	*9.9*	.002	66.3	*11.9*	66.6	*9.8*	.671	64.0	*11.4*	66.6	*10.6*	.007
Occupational status, *N* (%)															
Unskilled	2	(0.6)	3	(0.7)	.030	12	(3.1)	13	(2.8)	.041	17	(7.4)	19	(6.4)	.129
Partly skilled	13	(3.7)	31	(7.7)		24	(6.3)	50	(10.9)		28	(12.2)	47	(15.7)	
Skilled manual	43	(12.1)	31	(7.7)		54	(14.1)	57	(12.4)		53	(23.1)	56	(18.7)	
Skill non-manual	75	(21.1)	71	(17.6)		68	(17.8)	106	(23.0)		41	(17.9)	78	(26.1)	
Intermediate	171	(48.2)	218	(54.1)		161	(42.0)	176	(38.3)		72	(31.4)	74	(24.7)	
Professional	51	(14.4)	49	(12.2)		64	(16.7)	58	(12.6)		18	(7.9)	25	(8.4)	

Note. Values are means and *SD (italics)*, except for categorical variables where group sizes (and percentages) are shown. Sample sizes vary according to missing data on each variable.
[a] Chi-squared test was used for dichotomous variable group differences (e.g. smoking), and *t*-tests were conducted on all other variables which were treated as continuous variables; log-transformed values of the reaction times were used.

Table 6.3 Regression coefficients (and 95% CI) for associations between baseline reaction times and inflammation after 20 years: Men.

	CRP				Fibrinogen			
	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd
1972 cohort			*N* = 329 to 330				*N* = 323 to 325	
Model 1	.038 [-.013, .089] *p* = .139	-.003 [-.045, .040] *p* = .903	**.058 [.011, .104] *p* = .015**	**.071 [.027, .116] *p* = .002**	.049 [-.021, .119] *p* = .170	.022 [-.037, .080] *p* = .466	.004 [-.061, .069] *p* = .903	.008 [-.054, .071] *p* = .795
Model 2	.005 [-.044, .054] *p* = .837	-.017 [-.058, .028] *p* = .403	.027 [-.019, .072] *p* = .254	.043 [-.001, .087] *p* = .054	.039 [-.033, .111] *p* = .288	.016 [-.043, .074] *p* = .598	-.007 [-.074, .059] *p* = .828	-.002 [-.066, .062] *p* = .951
Model 3	.003 [-.047, .052] *p* = .914	-.018 [-.059, .022] *p* = .373	.024 [-.022, .070] *p* = .315	.040 [-.005, .084] *p* = .080	.040 [-.032, .113] *p* = .271	.016 [-.043, .075] *p* = .587	-.006 [-.073, .061] *p* = .860	.000 [-.065, .065] *p* = .998
Model 4	-.005 [-.055, .045] *p* = .837	-.024 [-.065, .017] *p* = .246	.018 [-.028, .064] *p* = .446	.034 [-.011, .079] *p* = .135	.022 [-.050, .093] *p* = .554	.004 [-.054, .062] *p* = .886	-.020 [-.086, .047] *p* = .558	-.014 [-.078, .051] *p* = 680
1952 cohort			*N* = 348 to 353				*N* = 343 to 348	
Model 1	.026 [-.024, .076] *p* = .303	-.003 [-.058, .052] *p* = .916	.029 [-.017, .076] *p* = .215	.019 [-.027, .065] *p* = .425	**.111 [.035, .187] *p* = .004**	**.090 [.009, .171] *p* = .030**	**.081 [.009, .152] *p* = .027**	.054 [-.017, .125] *p* = .135
Model 2	.012 [-.038, .063] *p* = .633	-.018 [-.073, .036] *p* = .513	.007 [-.041, .056] *p* = .767	.004 [-.042, .050] *p* = .864	**.105 [.029, .181] *p* = .007**	.070 [-.010, .150] *p* = .087	.060 [-.013, .134] *p* = .108	.026 [-.044, .096] *p* = .463
Model 3	.006 [-.044, .056] *p* = .822	-.015 [-.068, .039] *p* = .595	.002 [-.046, .050] *p* = .937	.002 [-.044, .047] *p* = .941	**.105 [.029, .181] *p* = .007**	.071 [-.009, .151] *p* = .084	.060 [-.014, .134] *p* = .113	.026 [-.044, .096] *p* = .469
Model 4	.001 [-.049, .050] *p* = .979	-.025 [-.078, .028] *p* = .356	-.003 [-.050, .044] *p* = .903	-.010 [-.056, .035] *p* = .657	**.097 [.023 , .170] *p* = .010**	.054 [-.024, .132] *p* = .172	.054 [-.018, .126] *p* = .140	.016 [-.054, .085] *p* = .658

1932 cohort				*N* = 203				*N* = 197		
Model 1	.009 [-.043, .061] *p* = .734	-.018 [-.076, .040] *p* = .549	.029 [-.042, .101] *p* = .421	**-.080 [-.146, -.015]** ***p* = .017**	**-.126 [-.232, -.020]** ***p* = .020**	-.116 [-.234, .003] *p* = .056	-.062 [-.025, .081] *p* = .393	.033 [-.102, .167] *p* = .631
Model 2	-.026 [-.082, .030] *p* = .362	-.047 [-.108, .014] *p* = .131	-.013 [-.089, .062] *p* = .724	**-.093 [-.157, -.028]** ***p* = .005**	**-.142 [-.256, -.029]** ***p* = .015**	-.105 [-.231, .020] *p* = .100	-.083 [-.234, .068] *p* = .279	.017 [.118, -.152] *p* = .806
Model 3	-.029 [-.085, .028] *p* = .316	-.051 [-.112, .011] *p* = .104	-.017 [-.093, .059] *p* = .653	**-.095 [-.160, -.030]** ***p* = .004**	**-.154 [-.269, -.040]** ***p* = .009**	-.119 [-.246, .007] *p* = .065	-.098 [-.251, .054] *p* = .204	.010 [-.126, .145] *p* = .889
Model 4	-.032 [-.090, .025] *p* = .264	-.052 [-.113, .010] *p* = .101	-.020 [-.096, .056] *p* = .601	**-.096 [-.162, -.030]** ***p* = .004**	**-.152 [-.264, -.039]** ***p* = .009**	-.108 [-.219, .060] *p* = .090	-.090 [-.239, .058] *p* = .233	-.012 [-.146, .123] *p* = .864

Note. Statistically significant coefficients are in bold ($p < .05$). Higher reaction times are slower (m) and less consistent (sd). Model 1 is the basic model adjusting for age at w1, and weighted for attrition; Model 2: Basic model + baseline CVD covariates (smoking and occupational status, plus heart rate in 1952 cohort, and WHR in 1932 cohort); Model 3: Model 2 + education; Model 4: Model 3 + wave5 covariates.

Table 6.4 Regression coefficients (and 95% CI) for associations between baseline reaction times and inflammation after 20 years: Women

	CRP				Fibrinogen			
	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd
1972 cohort		*N* = 383-4				*N* = 378-9		
Model 1	-.004 [-.056, .047] *p* = .871	**.095 [.042, .148]** ***p* < .001**	.037 [-.015, .089] *p* = .165	-.008 [-.057, .040] *p* = .739	-.013 [-.084, .059] *p* = .720	-.017 [-.088, .056] *p* = .644	.041 [-.027, .109] *p* = .448	.032 [-.036, .099] *p* = .357
Model 2	-.014 [-.066, .037] *p* = .584	**.083 [.030, .136]** ***p* = .002**	.022 [-.031, .076] *p* = .407	-.016 [-.064, .033] *p* = .527	-.028 [-.100, .044] *p* = .452	-.033 [-.105, .039] *p* = .370	.022 [-.048, .091] *p* = .544	.021 [-.047, .090] *p* = .542
Model 3	-.025 [-.077, .026] *p* = .331	**.077 [.023, .131]** ***p* = .008**	.000 [-.054, .054] *p* = .995	-.038 [-.087, .011] *p* = .130	-.039 [-.111, .033] *p* = .286	-.047 [-.119, .025] *p* = .200	.000 [-.071, .070] *p* = .997	.001 [-.068, .070] *p* = .969
Model 4	-.022 [-.075, .030] *p* = .402	**.082 [.027, .137]** ***p* = .005**	.006 [-.049, .061] *p* = .830	-.035 [-.085, .015] *p* = .166	-.034 [-.107, .039] *p* = .359	-.039 [-.113, .035] *p* = .296	.001 [-.070, .074] *p* = .969	.006 [-.064, .076] *p* = .867
1952 cohort		*N* = 425-30				*N* = 415-20		
Model 1	.020 [-.026, .067] *p* = .386	.023 [-.022, .068] *p* = 309	.024 [-.026, .073] *p* = .344	-.004 [-.051, .044] *p* = .882	-.031 [-.099, .037] *p* = .366	.003 [-.063, .070] *p* = .920	.024 [-.049, .096] *p* = .518	.012 [-.059, .083] *p* = .741
Model 2	-.003 [-.049, .043] *p* = .900	.004 [-.041, .048] *p* = .873	-.017 [-.069, .034] *p* = .504	-.025 [-.073, .023] *p* = .311	-.044 [-.114, .025] *p* = .212	-.004 [-.072, .063] *p* = .897	-.005 [-.083, .072] *p* = .602	-.005 [-.079, .070] *p* = .897
Model 3	-.007 [-.053, .039] *p* = .774	.004 [-.040, .049] *p* = .843	-.021 [-.072, .030] *p* = .427	-.026 [-.074, .022] *p* = .293	-.045 [-.115, .023] *p* = .208	-.004 [-.072, .063] *p* = .899	-.006 [-.084, .072] *p* = .880	-.005 [-.080, .070] *p* = .892
Model 4	-.006 [-.051, .038] *p* = .776	.008 [-.034, .051] *p* = .703	-.031 [-.080, .019] *p* = .224	-.037 [-.083, .009] *p* = .118	-.046 [-.115, .022] *p* = .187	.003 [-.063, .069] *p* = .929	-.024 [-.269, .180] *p* = .537	-.020 [-.093, .054] *p* = .596

1932 cohort			*N* = 275-7				*N* = 265-7	
Model 1	.005 [-.035, .044] *p* = .816	.020 [-.027, .066] *p* = .409	-.004 [-.049, .041] *p* = .853	-.010 [-.053, .033] *p* = .650	-.005 [-.079, .068] *p* = .885	.061 [-.028, .149] *p* = .178	-.041 [-.125, .042] *p* = .330	-.020 [-.101, .061] *p* = .623
Model 2	.002 [-.040, .043] *p* = .937	.020 [-.027, .066] *p* = .404	-.008 [-.056, .041] *p* = .761	-.011 [-.055, .033] *p* = .610	-.020 [-.097, .057] *p* = .612	.059 [-.029, .147] *p* = .191	-.054 [-.144, .036] *p* = .241	-.023 [-.106, .059] *p* = .577
Model 3	-.002 [-.044, .040] *p* = .920	.018 [-.028, .065] *p* = .437	-.017 [-.067, .032] *p* = .494	-.019 [-.064, .025] *p* = .394	-.022 [-.099, .056] *p* = .584	.059 [-.030, .147] *p* = .192	-.060 [-.152, .032] *p* = .199	-.028 [-.112, .057] *p* = .520
Model 4	-.016 [-.058, .027] *p* = .469	.011 [-.035, .057] *p* = .633	-.024 [-.074, .025] *p* = .337	-.013 [-.057, .031] *P* *p* = .570	-.009 [-.089, .071] *p* = .831	.070 [-.019, .159] *p* = .122	-.055 [-.149, .039] *p* = .249	-.034 [-.119, .050] *p* = .425

Note. Statistically significant coefficients are in bold ($p < .05$). Higher reaction times are slower (m) and less consistent (sd). Model 1 is the basic model adjusting for age at wave1, and relevant dummy variable at wave5 (oral contraceptive use among 1972 cohort; HRT use among 1952 cohort), and weighted for attrition; Model 2: Model 1 + baseline CVD covariates (smoking and occupational status, plus heart rate in 1952 cohort, and WHR in 1932 cohort); Model 3: Model 2 + education; Model 4: Model 3 + wave5 covariates.

Table 6.5 Odds ratios (and 95% CI) for high CRP, predicted by baseline reaction times: Men.

	1972 cohort *N* = 331				1952 cohort *N* = 351				1932 cohort *N* = 203			
	SimpleRT m	SimpleRT *SD*	ChoiceRT m	ChoiceRT *SD*	SimpleRT m	SimpleRT *SD*	ChoiceRT m	ChoiceRT *SD*	SimpleRT m	SimpleRT *SD*	ChoiceRT m	ChoiceRT *SD*
Model 1	**0.79 (0.66, 0.94) *p* = .009**	1.08 (0.90, 1.28) *p* = .407	**0.71 (0.60, 0.86) *p* < .001**	**0.78 (0.66, 0.93) *p* = .004**	0.84 (0.69, 1.03) *p* = .090	0.95 (0.76, 1.20) *p* = .674	0.94 (0.78, 1.14) *p* = .544	1.03 (0.86, 1.25) *p* = .733	0.88 (0.72, 1.06) *p* = .172	1.09 (0.88, 1.35) *p* = .422	0.84 (0.65, 1.10) *p* = .200	**2.01 (1.47, 2.74) *p* < .001**
Model 2	0.93 (0.77, 1.13) *p* = .478	1.18 (0.99, 1.40) *p* = .072	0.85 (0.70, 1.03) *p* = .102	0.93 (0.77, 1.11) *p* = .396	0.90 (0.73, 1.11) *p* = .304	1.01 (0.80, 1.27) *p* = .854	1.05 (0.85, 1.29) *p* = .652	1.13 (0.92, 1.39) *p* = .234	1.04 (0.84, 1.29) *p* = .726	**1.35 (1.04, 1.75) *p* = .024**	1.05 (0.79, 1.40) *p* = .746	**2.08 (1.52, 2.85) *p* < .001**
Model 3	0.94 (0.77, 1.14) *p* = .532	1.18 (0.99, 1.41) *p* = .066	0.86 (0.71, 1.05) *p* = .128	0.94 (0.78, 1.12) *p* = .481	0.91 (0.74, 1.13) *p* = .387	.01 (0.80, 1.28) *p* = .950	1.07 (0.87, 1.32) *p* = .523	1.14 (0.93, 1.40) *p* = .201	1.08 (0.86, 1.34) *p* = .521	**1.42 (1.10, 1.85) *p* = .008**	1.09 (0.82, 1.47) *p* = .550	**2.14 (1.56, 2.93) *p* < .001**
Model 4	0.96 (0.73, 1.30) *p* = .696	1.18 (0.87, 1.49) *p* = .067	0.85 (0.64, 1.13) *p* = .139	0.88 (0.67, 1.16) *p* = .423	0.93 (0.75, 1.15) *p* = .494	1.06 (0.83, 1.35) *p* = .664	1.10 (0.89, 1.36) *p* = .383	1.22 (0.99, 1.52) *p* = .066	1.10 (0.88, 1.38) *p* = .398	**1.43 (1.10, 1.87) *p* = .008**	1.11 (0.83, 1.49) *p* = .491	**2.09 (1.52, 2.87) *p* < .001**

Note. All models include an inverse probability weighting to account for attrition bias. Reaction time variable scores were reversed, so that lower values indicate slower and more variable performance. *OR* in bold is significant, $p < .05$. Model 1 is the basic model and adjusts for age at wave1; Model 2: Model 1 + baseline CVD covariates (smoking and occupational status, plus heart rate in the 1952 cohort and WHR in the 1932 cohort); Model 3: Model 2 + education; Model 4: Model 3 + wave5 covariates. *m* = mean reaction time speed; *sd* = reaction time standard deviation (consistency); CVD risk = current smoking and occupational status, plus heart rate in 1952 cohort, and WHR in 1932 cohort
There were no issues of multicollinearity.

Table 6.6 Odds ratios (and 95% CI) for high CRP, predicted by baseline reaction times: Women

	1972 cohort *N* = 335				1952 cohort *N* = 429				1932 cohort *N* = 275			
	SimpleRT m	SimpleRT *SD*	ChoiceRT m	ChoiceRT *SD*	SimpleRT m	SimpleRT *SD*	ChoiceRT m	ChoiceRT *SD*	SimpleRT m	SimpleRT *SD*	ChoiceRT m	ChoiceRT *SD*
Model 1	0.96 (0.82, 1.13) *p* = .631	**0.69 (0.58, 0.83) *p* < .001**	0.93 (0.79, 1.09) *p* = .378	1.05 (0.90, 1.23) *p* = .553	**0.85 (0.72, 0.99) *p* = .036**	0.87 (0.74, 1.02) *p* = .088	**0.82 (0.70, 0.97) *p* = .022**	0.94 (0.80, 1.10) *p* = .408	1.11 (0.94, 1.31) *p* = .209	1.02 (0.84, 1.22) *p* = .862	1.07 (0.89, 1.27) *p* = .493	1.05 (0.88, 1.24) *p* = .589
Model 2	0.98 (0.83, 1.15) *p* = .806	**0.70 (0.58, 0.84) *p* < .001**	0.96 (0.81, 1.13) *p* = .588	1.07 (0.91, 1.26) *p* = .424	0.91 (0.77, 1.08) *p* = .281	0.93 (0.79, 1.10) *p* = .417	0.95 (0.80, 1.14) *p* = .583	1.01 (0.86, 1.20) *p* = .871	1.17 (0.98, 1.39) *p* = .084	1.01 (0.84, 1.22) *p* = .913	1.11 (0.91, 1.36) *p* = .286	1.06 (0.89, 1.27) *p* = .493
Model 3	1.02 (0.87, 1.20) *p* = .814	**0.73 (0.61, 0.87) *p* < .001**	1.03 (0.87, 1.23) *p* = .710	1.16 (0.98, 1.37) *p* = .092	0.92 (0.78, 1.09) *p* = .319	0.93 (0.79, 1.10) *p* = .409	0.96 (0.80, 1.15) *p* = .633	1.01 (0.86, 1.20) *p* = .871	**1.20 (1.01, 1.44) *p* = .044**	1.02 (0.84, 1.24) *p* = .855	1.19 (0.97, 1.46) *p* = .096	1.12 (0.93, 1.35) *p* = .217
Model 4	0.91 (0.71, 1.16) *p* = .992	**0.71 (0.56, 0.96) *p* < .001**	0.98 (0.77, 1.25) *p* = .872	1.12 (0.89, 1.43) *p* = .124	0.92 (0.78, 1.09) *p* = .328	0.91 (0.77, 1.09) *p* = .307	0.99 (0.83, 1.19) *p* = .924	1.05 (0.88, 1.24) *p* = .590	**1.34 (1.10, 1.62) *p* = .003**	1.06 (0.87, 1.29) *p* = .579	**1.25 (1.01, 1.54) *p* = .040**	1.10 (0.91, 1.32) *p* = .333

Note. All models include an inverse probability weighting to account for attrition bias. Reaction time variable scores were reversed, so that lower values indicate slower and more variable performance. ORs in bold are statistically significant at $p < .05$. Model 1 is the basic model and adjusts for age at wave1 and wave5 dummy variables (oral contraceptive use in 1972 cohort; HRT use in 1952 cohort); Model 2: Model 1 + baseline CVD covariates (smoking and occupational status, plus heart rate in 1952 cohort, and WHR in 1932 cohort); Model 3: Model 2 + education; Model 4: Model 3 + wave5 covariates. *m* = mean reaction time speed; *sd* = reaction time standard deviation (consistency); CVD risk = current smoking and occupational status, plus heart rate in 1952 cohort, and WHR in 1932 cohort

There were no issues of multicollinearity.

Table 6.7 Stability of cognitive measures between wave1 and wave5.

	1972 cohort		1952 cohort		1932 cohort	
	Men *N* = 337-339	Women *N* = 388-389	Men *N* = 358-361	Women *N* = 438-440	Men *N* = 192-211	Women *N* = 241-280
SimpleRT m	.33 *p* < .001	.33 *p* < .001	.44 *p* < .001	.35 *p* < .001	.25 *p* < .001	.29 *p* < .001
SimpleRT sd	.09 *p* = .095	.12 *p* = .020	.21 *p* < .001	.27 *p* < .001	.11 *p* = .120	.17 *p* = .005
ChoiceRT m	.52 *p* < .001	.55 *p* < .001	.62 *p* < .001	.59 *p* < .001	.43 *p* < .001	.37 *p* < .001
ChoiceRT sd	.33 *p* < .001	.32 *p* < .001	.40 *p* < .001	.37 *p* < .001	.16 *p* = .028	.28 *p* < .001
AH4 score					.80 *p* < .001	.82 *p* < .001

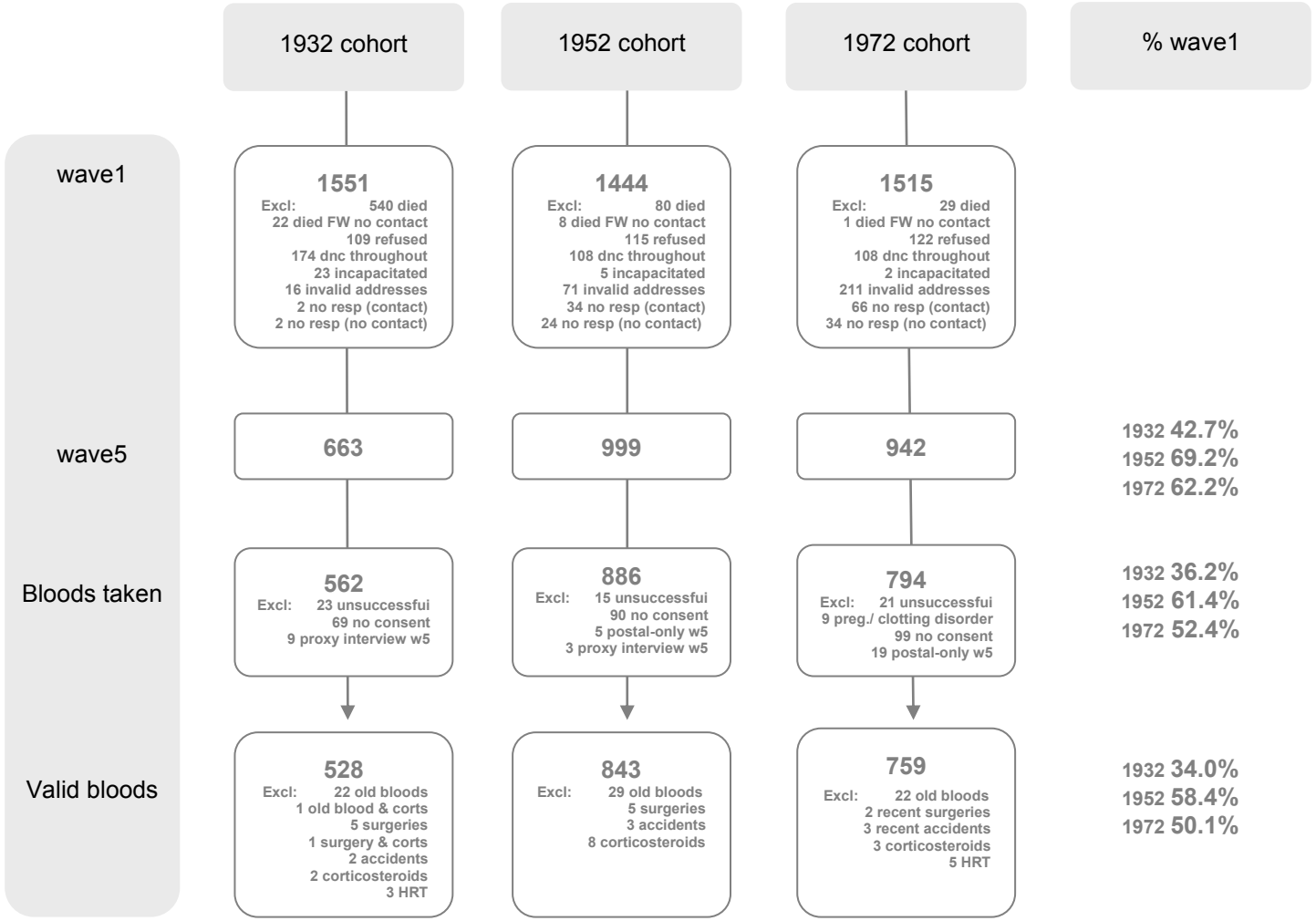
Note. Values are Pearson's r coefficients.

Table 6.8 Regression coefficients (and 95% CI in parenthesis) for contemporaneous associations between reaction times and inflammatory biomarkers.

	CRP				Fibrinogen			
	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd
1972 cohort			*N* = 713-5				*N* = 703-5	
Model 1	-.004 [-.016, .008] *p* = .453	.021 [-.014, .055] *p* = .238	.006 [-.002, .014] *p* = .152	.013 [-.004, .030] *p* = .127	-.003 [-.012, .006] *p* = .542	-.002 [-.028, .024] *p* = .859	-.001 [-.007, .005] *p* = .678	.006 [-.007, .019] *p* = .330
Model 2	-.006 [-.017, .005] *p* = .254	.017 [-.017, .051] *p* = .336	.001 [-.006, .008] *p* = .859	.008 [-.008, .024] *p* = .330	-.003 [-.011, .005] *p* = .449	-.004 [-.030, .022] *p* = .786	-.003 [-.008, .002] *p* = .291	.005 [-.007, .017] *p* = .430
1952 cohort			*N* = 788				*N* = 778	
Model 1	**.020 [.007, .033] *p* = .002**	.033 [-.007, .072] *p* = .109	**.017 [.008, .026] *p* < .001**	**.042 [.023, .061] *p* < .001**	**.011 [.002, .019] *p* = .020**	.017 [-.011, .044] *p* = .232	**.006 [.000, .012] *p* = .045**	**.018 [.005, .031] *p* = .006**
Model 2	**.017 [.005, .029] *p* = .005**	.031 [-.008, .070] *p* = .115	**.013 [.006, .020] *p* < .001**	**.041 [.024, .059] *p* < .001**	**.009 [.001, .017] *p* = .029**	.014 [-.012, .041] *p* = .284	.004 [-.001, .009] *p* = .148	**.016 [.004, .028] *p* = .010**
1932 cohort			*N* = 486				*N* = 469	
Model 1	.017 [-.013, .048] *p* = .267	.021 [-.057, .100] *p* = .595	.017 [-.003, .036] *p* = .098	**.050 [.004, .096] *p* = .031**	-.012 [-.029, .004] *p* = .135	-.030 [-.071, .012] *p* = .159	-.010 [-.021, .001] *p* = .068	-.014 [-.040, .011] *p* = .271
Model 2	.015 [-.015, .045] *p* = .314	.023 [-.055, .100] *p* = .564	.014 [-.004, .032] *p* = .137	**.062 [.017, .106] *p* = .006**	-.009 [-.025, .007] *p* = .272	-.028 [-.069, .013] *p* = .182	-.008 [-.018, .002] *p* = .127	-.012 [-.036, .013] *p* = .352

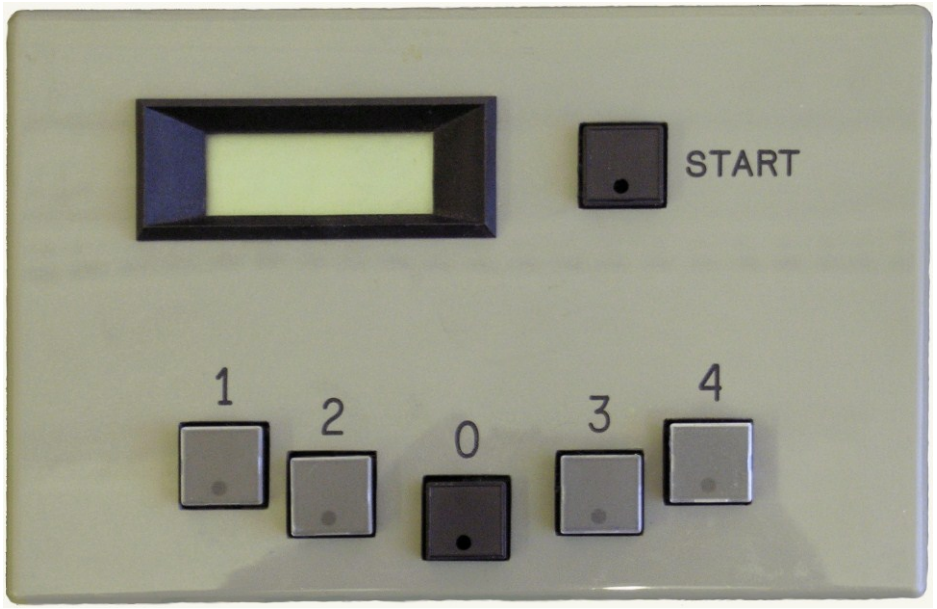
Note. All models are weighted for attrition. Model 1 and 2 match on sample sizes for each association. The regression coefficient is the effect of a one unit change in biomarker value in relation to a log-transformed unit change in the reaction time variable. Model 1 is the basic model adjusting for sex, age at wave5, and dummy variables at wave5 (oral contraceptive among 1972 cohort; HRT among 1952 cohort); Model 2 is model 1 + adjustment for the corresponding reaction time-variable measured 20 years earlier. Coefficients marked bold are significant ($p < .05$).

Figure 6.1 Flow diagram of sample selection: Twenty-07.



Note. dnc = do not contact due to withdrawal; HRT = hormone replacement therapy.

Figure 6.2 Reaction time box used in the Twenty-07 study.



Chapter 7
Reaction time and the metabolic syndrome after 20 years: West of Scotland Twenty-07 Study

Chapters 5 and 6 investigated cognition in relation to systemic inflammation, which belongs to a series of pathogenic mechanisms that potentially pose biological risk throughout human ageing (Seeman et al., 2010). A closely related cluster of parameters showing associations with psychometric intelligence, and the focus of this chapter, are the metabolic syndrome (MetS) biomarkers. The collective burden of these risk factors for cardiovascular disease has been acknowledged since the 1920s (Eckel, Grundy, & Zimmet, 2005). The condition constitutes physical and biological risk parameters that include abdominal obesity, hyperglycaemia, hypertension, and dyslipidaemia (including high triglycerides and low HDL cholesterol). Metabolic syndrome is a precursor to life-threatening disease onset including type 2-diabetes (Ford, Li, & Sattar, 2008) and cardiovascular disease (Khunti & Davies, 2005), and is significantly related to premature mortality (Mottillo et al., 2010). That it has substantial prevalence in population-based cohorts, that it is evident at a preclinical stage of disease, and that it is detectable in younger and more representative adult populations, makes MetS an obvious endpoint in itself to study in relation to premorbid cognition, and lends itself to better understanding the pathways from intelligence to CVD-related outcomes.

Two previous studies have reported significant associations between psychometric intelligence in youth and later risk of metabolic syndrome, in cohorts from the UK and US. The present chapter reports for the first time on the longitudinal associations between low-level cognitive processing speed (as seen in the previous chapter) and metabolic risk 20 years later, using the west of Scotland Twenty-07 cohorts.

Psychometric intelligence and metabolic risk

Longitudinal cohort data have demonstrated significant associations between lower scores on psychometric intelligence in youth, and individual metabolic risk factors, including high blood pressure, low HDL cholesterol, high waist circumference, high glycated haemoglobin, and high triglycerides (Chandola et al., 2006; Hart et al., 2004; Power, Jeffries, & Manor, 2010; Richards et al., 2009; Starr et al., 2004). These studies report mediation by education, socioeconomic status, and/or lifestyle behaviours, as largely explaining the association, although sometimes the effect remains robust of full statistical adjustment, for example in the case of blood pressure (Starr et al., 2004). Others however, report null effects in unadjusted models, for example in the association between intelligence differences, and total cholesterol or blood glucose (Hart et al., 2004). Given that such metabolic risk factors often cluster together statistically (Batty, Gale, et al., 2008; Pladevall et al., 2006), particularly with increasing age (Ervin, 2009; Kraja et al, 2006), it has been of interest to consider the effect of intelligence differences in predicting later risk for MetS.

Premorbid intelligence and the metabolic syndrome

To date two published studies have reported on the association between general cognitive ability in youth and the clustering of metabolic risk factors in adulthood. The first, the Vietnam Experience Study of over 4,000 male army veterans, used intelligence test scores (Army General Technical or AGT Test) at army entry, at a mean age of 20 years, and data from clinical examination 18 years later (in 1986), which included measurement of risk factors for MetS (Batty, Gale, et al., 2008). The cohort was a randomly selected subgroup from >18,000 army personnel, representing 23% of the original sample. The AGT test scores showed significant inverse associations with four out of five MetS risk factors that included hypertension, high body mass index (BMI), high triglycerides and high blood glucose. There was no association with HDL-cholesterol. Batty, Gale, et al. (2008) reported that a one *SD* advantage in intelligence test scores was significantly associated with a 14% reduced odds of MetS. However, unlike the literature on individual metabolic risk factors, this effect was not accounted for by prior

educational experience or achievement, nor was it explained by socioeconomic factors including income, social prestige, and army rank.

The second report, of the 1946 British Birth Cohort study, had greater longitudinal follow-up, relating intelligence test scores collected at age eight to metabolic risk factors when participants were age 53 years (Richards et al., 2009). This study's large-scale psychometric intelligence testing in youth provided greater confidence that cognitive performance was a 'premorbid' measure, less likely to be affected by lifestyle behaviours or educational inequalities that also contribute to metabolic syndrome risk (Langenberg, Kuh, Wadsworth, Brunner, & Hardy, 2006; Wilsgaard & Jacobsen, 2007). Therefore any observed association would be at lower risk of confounding by these factors, relative to studies where collection of baseline cognitive measures begins in adulthood. Compared to the US Vietnam veterans the participants of the 1946 British Birth Cohort study were also more nationally representative; they included both men and women and had broader socioeconomic spread. Despite these important differences in study design, Richards et al. (2009) replicated the result of the U.S. study, reporting an equivalent effect size among nearly 1,800 cohort members; a significant 14% reduced odds of MetS risk given a one *SD* advantage in intelligence test scores.

An inconsistency between these two studies however was the mediating effect of education. In the British cohort educational attainment by age 26 entirely accounted for the association between intelligence and MetS. That is, after adjusting for the highest educational qualification achieved by individuals the association was fully attenuated, implying a mediation effect. Whereas Batty, Gale, et al. (2008) who controlled for total years spent in education among the individuals in their cohort, observed no such dent in the effect size.

Understanding pathways from IQ to MetS risk

It therefore remains unclear as to the mechanistic pathway(s) linking cognitive ability in youth to metabolic risk in adulthood. There may be, for example, a sex differential in explaining the effect, given evidence that education is more predictive of MetS in women versus men (Wilsgaard & Jacobsen, 2007); in the

British cohort that included women, education was an important covariate (Richards et al., 2009), relative to the men-only cohort (Batty, Gale, et al., 2008). Furthermore, the previous two studies tested mediation via educational and socioeconomic inequalities, yet perhaps independent of these, lifestyle behaviours may explain additional variance.

A problematic issue (and theme throughout this thesis) of including socioeconomic variables in models where intelligence (as an independent variable) correlates strongly with such factors, is one of statistical overadjustment. In this case attenuation effects that result from the addition of SES to a model, interpreted as mediation or confounding, may be overinflated. To overcome this particular issue, the present study makes use of the west of Scotland Twenty-07 study, which as explained in the previous chapter, has cognitive processing speed measures rather than the more frequently available psychometric intelligence scores. These reaction times are more independent of socioeconomic indices than the latter, enabling a reduction in risk of overadjustment in models that control for education and SES. This therefore allows for mediation effects to be tested more reliably with a range of covariates, on a pathway towards metabolic risk.

A potential pathway from processing speed to MetS

Alternative explanations of the pathway from intelligence differences to CVD-morbidities may obviously include confounding, and reverse causation, and statistical-adjustment for covariates to take account of these potential effects are essential. However, as discussed in previous chapters, the possibility of underlying system integrity as an alternative theory for the association remains a possibility. While it may only ultimately be tested by genetics research, epidemiological investigations can at the very least infer its likelihood. Given that processing speed is a more direct measure of neurological integrity than intelligence test performance (Penke et al., 2010), the present study can test (the plausibility at least of) a system integrity hypothesis in cognition—to—MetS associations. That is, if significant associations exist between cognitive processing speed and MetS, then an underlying cause of association between premorbid cognitive ability and metabolic function,

which predate lifestyle and social influence, remains a possibility. If however, a relation is not observed, associations between psychometric intelligence and metabolic risk reported in the literature can be more confidently interpreted as mediation by lifestyle behaviour and influence.

Processing speed and metabolic risk

Although this the first study to examine the association between individual differences in baseline reaction time and later MetS, previous studies have looked at the relationship contemporaneously or in the reverse direction; that is, the effect of MetS on subsequent cognitive function.

Cross-sectional evidence from case-control studies of adult patients with MetS versus healthy control groups suggest that psychometric and experimental processing speeds are significantly slower in cases compared to controls (Berg et al., 2008; Segura et al., 2009). Among the few population-based cohort studies investigating associations between metabolic risk factors and processing speed, diabetes and hyperglycaemia show contemporaneous associations with slower experimental reaction times and poorer performance on an alphabet-coding task (measuring information processing speed) respectively (Anstey et al., 2005; Dik et al., 2007). Such evidence implicates glucose control as a component of MetS that bears relation to cognitive speed. However, in a separate study of older non-diabetic men the glucose biomarker HbA1c was found to be unrelated to processing speed (MacLullich et al., 2004).

Another component of MetS is high blood pressure, and there has been less evidence for its relation to reaction time performance, including a cross-sectional study that reported a null association between hypertension and contemporaneous simple and choice reaction times (Anstey et al., 2005). Furthermore, a 12-year longitudinal investigation of older adults reported no effect of baseline MetS on later processing speed (Komulainen et al., 2007)—although the syndrome was associated with poorer memory performance.

Whereas the evidence is inconsistent and not yet substantive, there remains biological plausibility that MetS is a preclinical risk factor for vascular-related

cognitive decline (Segura et al., 2009). For example, adults with vascular risk profiles, including hypertension, relative to healthy controls, show longitudinal decline in cortical volume and an increase in white matter hypertensities, associated with cognitive decline (Raz, Rodrigue, Kennedy, & Acker, 2007). Therefore, the cluster of risk factors that constitutes MetS is most likely detrimental to cognitive function and neural health. However, if such an association is observed in older adult cohorts, a consideration of premorbid cognitive ability is also important; that is, an entirely causal effect of metabolic function on cognition should not be assumed. Looking at the association between metabolic risk and cognitive performance in reverse is therefore informative to cognitive ageing and cognitive epidemiology research.

The present study

The main aim of the present study is to test whether low-level cognitive performance measures at baseline—namely simple and choice reaction time speed and variability—relate to aspects of the metabolic syndrome 20 years later. This is investigated in three distinct age cohorts, and where the risk of confounding or reverse causation is lowest in the youngest, born in 1972, when processing speeds were recorded at age 16. The associations are investigated with attempts to account for reverse causation and to adjust for potentially confounding factors, and are further explored for mediation pathways that include adjustment for health behaviour indicators, education, and socioeconomic status.

Given the availability of processing speeds at wave5 in the Twenty-07 cohort—measured at the same time as metabolic risk factors—there is the additional opportunity to measure the contemporaneous relation between metabolic risk and processing speeds in three distinct age cohorts, and to test for potential reverse causation by adjusting for baseline reaction times. The results of this secondary analysis may be informative to cognitive ageing studies that consider cognitive decline as a consequence of vascular-related disease states, and to lifecourse epidemiology that must account for bidirectional associations among behavioural and

biological indices. It also provides opportunity to consider alternative explanations for the observations reported in cognitive epidemiology, such as system integrity.

Methods

Study population

The study cohorts from the west of Scotland Twenty-07 Study were described in detail in the methods section of chapter 6. In brief, these included three birth cohorts from 1972, 1952 and 1932, interviewed for the first time at approximately 16, 36 or 56 years of age (wave1). The present study (as in the previous chapter) uses 20-year follow-up data at wave5 to assess metabolic risk outcomes. Measures at baseline included cognitive testing, social status, and self-reported physical health measures. The cohorts in this chapter consist of participants who consented to give blood at wave5 and who had no missing data on the variables that assessed metabolic risk. Sample selection presented in chapter 6's flow diagram (Figure 6.1) is just as relevant to the cohorts used in the present chapter. Among an original baseline sample of 4,510 participants, 1,942 (43.1%) had complete data with which to assess MetS at wave5.

Cognitive measures

Simple and four-choice reaction time. The methods to assess mental processing speed were described in the previous chapter. The same four performance measures were used to predict metabolic syndrome in the present study, at baseline and at wave5. They are: (i) SimpleRT *m*, (ii) simpleRT *sd*, (iii) choiceRT *m*, (iv) choiceRT *sd*.

Psychometric intelligence. Alice Heim 4 test scores (AH4) were available at both waves for the 1932 birth cohort only (Heim, 1970). In models where cognition was a predictor variable I used the standardised score ($M = 0$, $SD = 1$) to enable

comparisons with effect sizes for intelligence and metabolic syndrome associations reported by previous studies (Batty, Gale, et al., 2008; Richards et al., 2009).

Metabolic risk

Metabolic syndrome

I assigned metabolic syndrome (MetS) status as a new variable, according to the presence of at least three out of five risk factors available in the Twenty-07 dataset. These match the risk factors that Richards et al (2009) used in their investigation of intelligence and MetS, and are based upon the US's National Cholesterol Education Program recommendations (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001), but modified due to the availability of glycated haemoglobin (HbA1c) instead of plasma glucose (Langenberg et al., 2006). The five risk factors are:

- Waist circumference >102 cm in men and >88 cm in women
- Systolic blood pressure ≥130 mmHg or ≥140 mmHg in the 1932 cohort
- Triglycerides ≥1.7 mmol/L
- High density lipoprotein (HDL) cholesterol <1.036 mmol/L in men and <1.295 mmol/L in women
- Glycated haemoglobin (HbA1c) in the top gender-specific quartile of each cohort's distribution

Triglycerides, HDL cholesterol and HbA1c were measured from nonfasted intravenous blood samples taken using an arm tourniquet. The lipids were analysed from a sample collected in 6mL plain tube (yellow), and HbA1c was analysed from a separate sample collected in 4mL EDTA tube (purple). As described in the previous chapter, blood analysis was conducted at the Department of Clinical Biochemistry at the Glasgow Royal Infirmary, Glasgow, Scotland, within four days of the samples being taken. The participants' systolic blood pressure (systolic BP) was measured

three times and I retained the third reading (based on the highest recorded arm) for analysis.

Before participants were rated for risk on the five metabolic factors, medication use necessitated adjustment of measures, including systolic BP, HDL cholesterol and HbA1c values. Table 7.1 lists the value constants applied to these biomarkers according to each specific medication. Whereas oral contraceptives are shown to alter levels of serum triglycerides and HDL cholesterol (Cauci et al., 2008), there is insufficient evidence to make systematic adjustments for its use. Instead, in the 1972 cohort where 91 participants reported taking oral contraceptives at wave5, I included a dummy variable as a covariate (1 = *oral contraceptive use*, 0 = *no oral contraceptives*). There were no reports of oral contraceptive use in the 1932 and 1952 cohorts at wave5.

Metabolic risk component

The five variables that constituted the above criteria for metabolic syndrome were entered in to principal components analysis, with the intention of extracting a single continuous factor score that could best account for the variance in metabolic syndrome risk. Data reduction within each of the three cohorts consistently showed the same result. That is, triglycerides, HDL cholesterol, waist circumference, and HbA1c all loaded highly on a single component, whereas systolic BP loaded on to a second component. Given that the literature on metabolic risk often makes the distinction between this former cluster of metabolic parameters and the cardiovascular system—that includes blood pressure (Juster, McEwan, & Lupien, 2010; McEwan, 1998)—I decided to remove the blood pressure variables from this part of the analyses. Instead, I derived a proxy measure of low-density lipoprotein (LDL) cholesterol (total cholesterol minus HDL cholesterol) and added this to the models to optimise the validity of a metabolic component. Before estimating LDL cholesterol, total cholesterol levels were adjusted where participants used statins (increase of 1.8mmol/L) and/or diuretics (decrease of 4%) at wave5.

Covariates

The wave1 and wave5 covariates listed in Chapter 6 were also tested for their associations with MetS or the metabolic component. (Appendix C reports on the associations between these outcome measures and the covariates within the three aged cohorts). The significant covariates at wave1 and wave5, in one or more cohorts[6], were *current smoking* status ('yes' = 1, 'no' = 0), *occupational status* as the SES variable (1 to 6 categories where 1 = unskilled and 6 = professional), and *heart rate*. *Waist-to-hip ratio* (WHR) was an additional covariate at wave1. At wave5 education was recorded based upon total number of years in *full-time education*.

Statistical analyses

Exclusion and outlier criteria

The same exclusion criteria as in Chapter 6 were applied to the data in the present study. First, I excluded choiceRT data from analyses where there was record of a 25% or greater error rate. Additional factors potentially affecting the validity of one or more risk factors associated with metabolic syndrome were: Accident or surgery within 31 days of blood sampling; blood samples analysed after four days' delay; use of oral corticosteroids; use of HRT. In such cases data were excluded, with the exception of the 1952 cohort participants on HRT; these women were retained in the analysis, and I adjusted for this medication by inclusion of the dummy variable.

Statistical models

Data distributions and transformations for the independent variables were described in the previous chapter's methods section. The metabolic component derived from PCA was normally distributed and already standardised. Analyses were based on the samples of participants with complete data for, one or more cognitive

[6] If a covariate was significant in one cohort only, it was still included in models of all cohorts, to enable a comparison between models' effects sizes of the different age groups.

measures at wave1; metabolic syndrome risk according to the five risk factors[7], or a metabolic component score; covariates at both waves as described in the previous section. Models were run for the separate age groups using *PASW Statistics 17*. After exploratory correlation analysis the hypotheses were tested in the following ways:

(1) Logistic regression modelled the associations between cognitive measures and risk for MetS. For this set of analyses I inverted reaction times so that faster and more consistent reaction times were reflected in higher values. My reasoning behind this was to enable comparisons with effect sizes from previous studies. Odds ratios with 95% CI were estimated in a basic model and subsequent covariate-adjusted models that tested the effects of potential confounders and mediators.

In a basic model (Model 1) age and sex were adjusted (as well as wave5 dummy variables for contraceptive and HRT use, explained in previous sections of these Methods).

A second model (Model 2) attempted to account for existing metabolic risk by adjusting for baseline WHR and heart rate (as a proxy for physical fitness), given that nothing else relevant to metabolic risk factors was collected at wave1. This model also adjusted for wave1 SES and smoking, which may have confounded the association.

Model 3 adjusted for education, as I was interested to see the extent of its attenuation effect on the model alone, given its strong mediation effects in the background literature.

Model 4, the final model, tested potential mediation effects by including wave5 covariates including SES, smoking, and heart rate. Changes in variance explained by odds ratios in adjusted models are calculated as a proportion of the odds ratio from the basic model.

(2) Principal components analysis was used to derive a single metabolic component within each cohort. Values from the first unrotated principal component were saved, and two sets of multiple regression analyses were run:

1. A one *SD* change in wave1 reaction times was modelled to predict the metabolic component value at wave5. A basic model and three

[7] If participant data were missing for one or two risk factors, a diagnosis of metabolic syndrome could still be made in the presence of three remaining risk factors.

subsequent adjusted models were run, using the same covariates and rationale as for the logistic regression models above.

2. The metabolic component was modelled to predict contemporaneous reaction times at wave5, before and after adjustment for wave1 reaction times—thereby testing for reverse causation.

For both sets of results, unstandardised regression coefficients and their 95% CI are tabulated. Unlike the logistic regression models to predict metabolic syndrome, where I inverted the RT data so as to make comparisons with previous studies' effect sizes, in linear regression models the RT data retained their raw form, that is, higher values reflected slower and less consistent performances. As in the previous chapter, partial correlations are reported to give an indication of effect size of the significant associations, as are estimates of change in the proportion of variance explained from basic to adjusted models:

$$\text{Partial } r^2_{\text{basic model}} - \text{partial } r^2_{\text{adjusted-model}} / \text{partial } r^2_{\text{basic model}}$$

In all models I included the inverse probability weight detailed in Appendix D, to account for attrition bias.

Results

Prevalence of metabolic syndrome

Prevalence rates for MetS are shown in Table 7.2, and are similar to population data (Khunti & Davies, 2005), albeit they are somewhat lower in the 1932 cohort compared to rates for over 60s in general populations (Ervin, 2009). The condition was higher among 56 and 76 year-olds (37.3 and 32.4%, respectively) compared to the 36 year-old-cohort (20.5%), consistent with longitudinal age trends showing a substantial shift from adults below 50 years to above (Ervin, 2009; Kraja et al, 2006).

Table 7.2 also includes group characteristics of those with and without MetS, within the three cohorts. A greater proportion of men than women were at risk of MetS in the 1972 cohort, $\chi^2(1) = 9.37$, $p = .002$, as well as in the 1952 cohort although the difference was non-significant. In the 1932 cohort the condition was more prevalent among women than men, although again this was only a trend effect. There were no group differences in proportions of smokers, either at baseline or wave5. In the 1972 and 1952 cohorts the syndrome was associated with lower occupational status at wave1, and in the 1952 cohort at wave5. Those with metabolic syndrome risk also showed higher WHR (1972 and 1952 cohorts only). Baseline heart rate was higher in those with MetS in the 1952 cohort, and was higher at wave5 among 1972 and 1952 cohort members with the condition. By follow-up those with MetS had been in education for less time than those without the condition, both in the 1972 and 1952 cohorts. In the 1932 cohort average educational years were greater in those with, versus those without, MetS. This effect was not significant, although it might indicate survivor bias in this oldest cohort.

Mean simple and choiceRT performances at wave1 were faster and less variable among those without MetS compared to those with the condition in the 1972 and 1952 cohorts, reaching statistical significance in the youngest cohort only. No significant group differences were observed on reaction time performance or the AH4 cognitive test score in the 1932 cohort.

Cognition and risk of MetS

Logistic regression models to predict MetS were conducted on the total cohorts rather than by sex group, given a lack of interaction effects between sex and RT. Table 7.3 displays the odds ratios for MetS according to baseline cognition, as measured by simple and choiceRT *m* and sd. As stated previously, the RT values were inverted so that faster and less variable performances were reflected in higher scores.

1972 cohort

In age- and sex-adjusted models of the 1972 cohort three out of four wave1 RT variables were predictive of MetS 20 years later. A one *SD* faster choiceRT and one *SD* more consistent simple- and choiceRT, were significantly associated with the reduced odds of the syndrome (*OR* 0.79, 0.82 and 0.89 respectively). In a second model that controlled for baseline CVD risk factors, the effect of choiceRT *sd* attenuated to non-significance (*OR* 0.92, 95% CI 0.82 to 1.04)—largely due to the effect of occupational status—and further adjustment for education attenuated the effect of mean choiceRT to non-significance (*OR* 0.90, 95% CI 0.79 to 1.03). However, the effect of simpleRT *sd* on MetS attenuated by ~25% only in a fully-adjusted model, and remained statistically significant (*OR* 0.79, 95% CI 0.71 to 0.89).

1952 cohort

Inverse associations were found between the four simple and choiceRT variables at age 36 and risk of MetS at age 56, in the 1952 cohort (*OR* 0.90 to 0.94), although these effects were not statistically significant ($p > .05$).

1932 cohort

In the 1932 cohort, simpleRT measures were unrelated to the risk of MetS and odds ratios were close to unity. However, in this older age cohort both choiceRT variables were positively associated with MetS. That is, faster and more consistent choiceRT at age 56 were associated with the increased risk of the condition by age 76 (choiceRT *m, OR* 1.49, 95% CI 1.19 to 1.87; choiceRT *sd, OR* 1.52, 95% CI 1.24 to 1.86). These effects were stable after full adjustment for covariates (choiceRT m, *OR* 1.44, 95% CI 1.13 to 1.84; choiceRT *sd, OR* 1.43, 95% CI 1.17 to 1.76). Consistent with these findings, a one *SD* advantage in AH4 scores at 56 years were associated with the increased risk of MetS at 76, in an age- and sex-adjusted model that included 321 participants with no missing values (*OR* 1.02, 95% CI 1.01 to 1.04, $p = .003$). Baseline covariates did not explain this effect; adjusting for the potential

mediating effects of SES and other CVD-risk factors did however attenuate the effect to non-significance (*OR* 1.01, 95% CI 0.99 to 1.04, $p = .33$).

A metabolic syndrome component

The results of principal components analysis of the five metabolic risk variables are presented in Table 7.4. It is clear from the scree plots that the first components derived for each of the three aged cohorts explained substantial variance compared to the four subsequent components, illustrated by an elbow at the second. The first component loading from the unrotated factor solution explained 50.1% of the variance in the 1972 cohort; it explained 44.4% of the variance in the 1952 cohort, and 37.5% of the variance in the 1932 cohort. Out of the five metabolic measures, triglycerides had the highest loading on the PCA component in all cohorts (.76 to .85), while HbA1c generally showed the lowest loadings across cohorts (.42 to .46). The component loading for LDL cholesterol was relatively high in the youngest cohort (.77), and showed an incremental decrease with older age cohorts (.61 and .46). This may be responsible for the incremental decline in total variance explained by the components of the youngest to oldest cohort, and could be due to LDL (or non-HDL) cholesterol being differentially affected by age. For example, high LDL cholesterol which is a risk factor for premature all-cause mortality in most of adulthood can show the reverse effect in adults above 65 years (Akerblom et al., 2008); at least in relation to vascular-related deaths LDL cholesterol carries a much weaker association compared to that in younger adults (Prospective Studies Collaboration, 2007).

Baseline cognition and the metabolic component

Table 7.5 shows the unstandardised regression coefficients and their 95% confidence intervals for predicting scores on the metabolic syndrome component according to baseline reaction times. The models were run for men and women combined, given the lack of any interaction effects between sex and RT in predicting

variance in the metabolic component.[8] The non-inverted RT values were modelled, so that higher values reflected slower and more variable simple and choiceRT.

1972 cohort

In the 1972 cohort, performances on the four RT measures were positively related to the metabolic component at wave5. That is, in a basic model that adjusted for age and sex, faster and more consistent reaction times at age 16 were significantly associated with lower metabolic component scores at age 36. The effect sizes as partial correlations (partial *r*) ranged from .14 to .40. The variances in the metabolic syndrome attributable to simpleRT *m* and *sd* were attenuated by 56% and 13% respectively, after simultaneous adjustment for baseline smoking, SES, heart rate and WHR, and which remained statistically significant. The effects of choiceRT *m* and *sd* in explaining variance in the metabolic component were largely attenuated after accounting for baseline covariates (82% and 76% respectively), yet these associations also remained statistically significant. In models that adjusted for each of the baseline covariates individually (data not reported), it was clear that the attenuation effect was largely due to SES; no effects of WHR and heart rate—to potentially account for reverse causation—were observed. Further adjustment for education made relatively modest changes to the effects. ChoiceRT variables were no longer associated with the metabolic component in fully adjusted models (ChoiceRT *m*, partial $r = .04$; ChoiceRT *sd*, partial $r = .05$), and mediation by SES was largely responsible for this additional attenuation. However, associations between simpleRT speed and consistency, and the metabolic component, which were further attenuated by 25% and 7% only after controlling for potentially mediating variables, retained statistical significance (SimpleRT *m*, partial $r = .10$; SimpleRT *sd,* partial $r = .36$).

1952 cohort

[8] One exception was in the 1972 cohort, where there was a significant interaction effect for Sex x SimpleRT *sd* (see Appendix H for chart). However the association was in the same direction for men and women and therefore I combined sex groups in all analysis.

In adults born around 1952, both simpleRT performance measures, and choiceRT *m,* were significantly associated with the metabolic system component. That is, faster and more consistent simpleRT at age 36, and faster choiceRT performance, related to lower scores on the metabolic component at age 56 (partial *r*, .09, .09 and .08 respectively). Attenuation effects for these three significant models were greatest when controlling for baseline CVD covariates (by 59%, 47%, and 90% respectively), after which the effect sizes were non-significant. Reverse causation appeared to be an unlikely explanation; that is, in models that adjusted for each of the adult risk factor covariates individually (data again not shown), neither WHR or heart rate had an attenuating effect; rather, low SES and to a smaller extent smoking, explained attenuation of the significant effects. Adjustment for mediating variables, including education and wave5 CVD covariates made negligible changes to the effect sizes from the baseline covariate-adjusted models.

1932 cohort

In the 1932 cohort there were no significant associations between reaction time variables and the metabolic component. The AH4 score at baseline positively related to the metabolic component at wave5, but again this was not statistically significant (coefficient = 0.03, 95% CI -0.06 to 0.11, $p = .51$).

Contemporaneous cognition and the metabolic component

Table 7.6 shows the beta coefficients and their 95% confidence intervals for contemporaneous associations between metabolic component scores and RT measures taken at wave5, before and after adjustment for wave1 RT. Again, non-inverted reaction times were used.

In the 1972 cohort at age 36, the metabolic component was positively associated with choiceRT but not simpleRT performances; that is, faster and more consistent choiceRT was significantly associated with lower metabolic component scores (partial $r = .13$ and .12 respectively). After control for equivalent baseline RT performance scores the associations were attenuated by 65% and 48% respectively

for speed and consistency, although remained statistically significant (partial r = .08 and .09).

In the 1952 cohort, at an average of 56 years, metabolic component scores were significantly and positively associated with three out of four RT variables (partial r = .08 to .12). The one exception was simpleRT *sd* (partial r = .05). After adjustment for baseline processing speed the relation to simpleRT *m* attenuated by 44% and was no longer significant. Associations between the metabolic component and choiceRT *m* and *sd* however, remained statistically significant after adjustment for their equivalent performance scores at wave1 (partial r = .10 and .11).

In the 1932 cohort, at an average age of 76, the metabolic component was unrelated to reaction time performance (partial r = -.04 to .01); neither did it relate to AH4 performance at wave5 (coefficient = -0.54, 95% CI -1.68 to 0.61, p = .36).

Discussion

This is the first investigation of longitudinal associations between reaction times and metabolic syndrome occurrence, in which the processing speed measure takes temporal precedence. The logistic regression models to predict MetS may be compared to previous investigations where an intelligence test score was the independent variable of interest. The magnitude of effects for one *SD* faster and more consistent reaction time performances at age 16 in relation to the reduced risk of MetS 20 years' later (*OR* in the range 0.77 to 0.90), are consistent with the two previous studies that each reported higher intelligence scores in youth relating to reduced metabolic risk in adulthood after 20 and 45 years respectively, at odds ratios of 0.86 in unadjusted models (Batty, Gale, et al., 2008; Richards et al., 2009). The weaker effect sizes among the present study's 1952 cohort, and the two unexpected positive associations in the older 1932 cohort, may be the result of confounding and/or an artefact of attrition; issues which are discussed in more detail further below. Given that reaction times in the youngest 1972 cohort would have been closest to optimal, relative to the two older cohorts where RT were measured at an age when processing speeds are already slowing (Der & Deary, 2006), it is these

results that arguably carry greater validity in testing the association between premorbid cognition and metabolic risk. In the 1972 cohort, reaction times were also significantly related to a metabolic component, albeit these were small effect sizes so that in the fully adjusted models cognitive speed explained <1% to 4% of the variance in this derived standardised score. Furthermore, reaction time performance at wave1 explained a substantial proportion of the significant contemporaneous associations between equivalent processing speed measures and the metabolic component at wave5, in the 1972 and 1952 cohorts. This finding demonstrates the likelihood of partial reverse causation in ageing studies that assess cognitive outcomes with processing speed parameters.

Cohort-specific effects

Age differential effects

The difference in study effects across the age groups are apparent between the older age group who were 76 years' old when assessed for MetS, versus the groups who were 36 years and 56 years when they were assessed on the same criteria for risk. Contrary to the present study's hypothesis, faster and less variable choice reaction times and higher intelligence test scores were associated with increased metabolic risk in the oldest cohort. However, that the prevalence of MetS in the oldest cohort was somewhat lower (particularly among men) compared to national prevalence rates for adults over 60 years (Ervin, 2009) is indicative of attrition or survivor bias. Evidence for the latter is the significantly lower mean waist circumference among survivors (M = 85.9 cm, SD = 11.3, n = 950) vs. non-survivors (M = 89.1 cm, SD = 12.9, n = 513) at baseline—when the 1932 cohort were 56 years' old (data not reported in Results).

Reasons for the association between superior reaction time performance and higher inflammatory status among the oldest cohort were reported in the previous chapter, including issues of sampling and measurement bias, ruling out the likelihood of a biological explanation for this reverse effect. Occupational status was also positively related to MetS in the 1932 cohort, which is again unexpected. However,

higher SES status that is normally related to the reduced risk of MetS in middle-aged groups has shown a null association with MetS in older adults (Loucks et al., 2007). Again, this might be attributed to attrition and survival bias in studies of older adults.

A specific cause of attrition bias in ageing research may be cognitive reserve (Stern, 2009), a theory asserting that in some individuals—particularly among groups with higher IQ and socioeconomic status—more adaptive processes allow for apparently stable or intact cognitive performance, despite evidence of neuropathology. Therefore, cohort members with the highest ability scores at baseline but who went on to develop metabolic system risk in older adulthood, may have had greater cognitive capacity with which to manage their condition, and, continue participation in the study, relative to those with lower baseline abilities.

That such positive associations between reaction times and metabolic syndrome in the 1932 cohort, were not observed for the metabolic component, is also revealing. The metabolic component excluded blood pressure data, and among participants that met criteria for MetS in this cohort, the frequency of hypertension was high relative to other risk factors. Therefore, this positive effect may be driven by, higher cognitive performers surviving (Deary & Der, 2005), and, continuing in the study despite high blood pressure.

Potential for sex differential effects

Given the lack of interaction effects of Sex x Reaction time in predicting metabolic risk, the present study combined men and women to optimise statistical power. Whereas in the previous chapter smoking was implicated as an apparent contributor to sex differentials in the effects of RT on systemic inflammation in the younger cohorts, it did not explain significant variance in the present study. Instead, baseline and wave5 SES made partial contributions to models. Given that metabolic risk differentially affects men and women however, particularly in respect to age, and that there are sex differentials on processing speed tasks (Der & Deary, 2006; Roivainen, 2011), it would be worth considering these two groups separately in future studies, where larger cohorts become available on men and women.

Prospective pathways from cognitive speed to metabolic risk

Where three reaction time measures significantly predicted MetS in the 1972 cohort, two of these associations remained robust after adjustment for potential confounders, and one (simpleRT sd) was robust against the further effects of education and wave5 covariates. This latter effect replicates results from the Vietnam Experience Study in which intelligence test scores retained relations to MetS risk in socioeconomic-adjusted models (Batty, Gale, et al., 2008), which was of a similar follow-up duration and age group to the present study, although included men only.

Lifestyle behaviours

Additional to socioeconomic indicators however, the present study considered lifestyle indicators to explain additional variance of the effect. Smoking did not contribute to the association between reaction times and MetS. Heart rate and WHR were controlled for, to try to account for metabolic risk at baseline, thus addressing reverse causation. However, they did not contribute to baseline-adjusted models. There are other lifestyle behaviours however that the present study could not account for. For example, dietary intake (including alcohol) may be a significant mediator, given that childhood intelligence has shown associations with adult dietary choices (Batty, Deary, Schoon, & Gale, 2007e; Gale et al., 2007), and that particular nutrient intake and excess fat consumption increase metabolic risk (Kimokoti & Brown, 2011). The Twenty-07 cohort does not have detailed data on participants' diets with which to evaluate this properly, but it is a lifestyle factor that deserves more thorough investigation.

A weaker role for education

Education explained far less of the variance in models predicting metabolic risk. However, given that education and SES are strongly correlated in the present study (r = .38 to .57), baseline occupational status that I adjusted for prior to

education, may have already removed any independent effects of education on the models.

In contrast, the previous British cohort study reported full mediation by education of the association between intelligence test scores at age eight and metabolic risk nearly 50 years later (Richards et al., 2009). The authors of this article suggested that the closer cognition and health outcomes are measured proximally to one another, the stronger an association is likely, due to common lifecourse influences. This implied that the non-attenuated effect reported from the Vietnam veterans' study of 20 year-olds, with 18-year follow-up, was less likely a direct association between cognition and metabolic risk, but rather a product of confounding. However, an alternative explanation is possible for the effects reported by Richards et al.; that is, given that the study's education and intelligence test scores correlated highly (r = .57) the importance of education in the model may have been an artefact of statistical overadjustment (Christenfeld, Sloan, Carroll, & Greenland, 2004). In the present study, using cognitive processing measures that held weaker associations with education in all three aged cohorts (r in the range -.28 to -.06) reduces the likelihood of overadjustment, making education an unlikely proxy for premorbid cognition. However, due to the closer proximity between the 1972 cohort's reaction time recordings and the end of their compulsory school term, there may be a greater chance that the small attenuation by education in the present study was due to confounding rather than mediation. That is, educational experience prior to age 16 may have contributed to both age 16 reaction times and age-36 metabolic risk, thus causing their indirect association.

To date however there remains little evidence as to whether educational experience may impact on processing speed at a population level, whereas there is rather more evidence that schooling can impact on psychometric intelligence performance (Deary & Johnson, 2010; Richards & Sacker, 2011). Reaction time-type tasks are not part of educational training, unlike pencil-and-paper testing—exposure to which could be part of improving IQ-test scores. However, whereas differential exposure to computer-assisted learning, or computer games, may theoretically affect individual differences in processing speed in present day, when the youngest participants from the Twenty-07 study were being educated in the late eighties, there

would have been limited exposure to information technology within or out with the classroom, for training effects to be of concern.

Another difference between the 1946 British Birth Cohort study and the present Twenty-07 study is in the prevalence rates of MetS. In the former metabolic syndrome was estimated at 21% among 53 year-olds. In comparison, and under the same criteria, I observed a rate of 37% among 56 year-old Glaswegians in the present study. This may have contributed to the different attenuation effect of education between the two studies. Of course another difference is that highest educational qualification was adjusted for in the Richards et al. study, whereas in the present study I adjusted for the total number of years in education.

Cognition to metabolic risk: Unexplained variance

I found little evidence for reverse causation (according to the variables available) in the forward association between baseline processing speeds and metabolic risk after two decades. Beyond partial attenuation by socioeconomic status at baseline and follow-up, direct effects between RT measures and metabolic risk were still observable in some models within the younger cohort. If all possible covariates were accounted for in the present study's models, then alternative explanations, including system integrity theory, remain a plausible explanation.

By extracting a single component from the constellation of metabolic system variables, thus optimising the variance in the data (rather than restricting it to a dichotomous variable comprised of arbitrary cut-offs – see Kahn, Buse, Ferrannini, & Stern, 2005), the number of significant effects in adjusted models were increased, including among the 1952 cohort. This methodological approach was used in the only study so far to consider MetS as a mediator in the association between psychometric intelligence and CVD-related mortality. The authors reported that a metabolic component explained 32% of the association, relative to a model where MetS was adjusted for and accounted for only 12% (Batty, Gale, et al., 2008). Clearly therefore, allowing for continuous variation in biological risk is informative to a field such as cognitive epidemiology, whether it ultimately reflects underlying system integrity or lifestyle factors. This approach is also consistent with the

construct of allostatic load, a single statistical continuous component that may explain dysregulation (or physiological instability) of multiple biological systems in response to psychosocial stressors, which include the metabolic syndrome and immune biomarkers. Allostatic load has been shown to have optimal predictive validity for morbidity and mortality risk, particularly cardiovascular-related risk, relative to separate system components (Juster et al., 2010; McEwan, 1998).

An underlying biological explanation for the association between processing speed and the metabolic component might be informed by differential effect sizes from the four reaction time tasks. For example, if choiceRT is more reflective of neuronal integrity than simpleRT performance (Penke et al., 2010) one might have expected relatively stronger effects of choiceRT with metabolic risk. Although choiceRT variables were associated with metabolic risk in basic models of the 1972 cohort, only the effects of simpleRT measures were robust against all covariates, particularly simple RT *sd*. In contrast, in contemporaneous associations at wave5 both choiceRT measures were associated with the metabolic component at 36 and 56 years of age, after adjustment for respective reaction time performances 20 years' earlier. This latter observation might either indicate lifecourse influences impacting neuronal and metabolic cellular processes in parallel, without necessarily direct linkage through antecedent system integrity, or, that alterations in the metabolic system are causal of processing speed slowing.

Collectively the aforementioned results could indicate that choiceRT is a closer indicator of alterations in neuronal integrity with ageing, relative to simpleRT performance that may be a more reliable indicator of premorbid cognition and neuronal integrity. Despite the low stability of simple RT *sd,* this processing speed measure was found to account for the majority of the association between age 11 intelligence test scores and an indicator of brain white matter integrity at age 83—centrum semiovale FA—leading the authors of this study to suggest that "efficiency of simple information processing might act as an intermediate phenotype" (Deary, Bastin, et al., 2006, p. 509), between psychometric intelligence and neuronal structure. The differentiation between simple and choice RT performances, in reflecting neuronal integrity throughout the life course, is therefore worthy of consideration.

Recent evidence suggests that differentiating between mean and variance measures of processing speed performance might also be informative to understanding associations with metabolic health. Mean reaction time compared to intraindividual variability, shows greater impairment in patients with type 2-diabetes relative to controls (Whitehead, Dixon, Hultsch, & MacDonald, 2011)—perhaps evidence for a bidirectional association between cognition and metabolism, mediated by glucose control (Stranahan & Mattson, 2011). However, in the present study's 1972 cohort, simpleRT speed and variability performed similarly in their significant associations with the metabolic component (while in fully-adjusted models both choiceRT variables performed similarly to each other in their lack of relatedness to metabolic risk). Furthermore, HbA1c showed the lowest component loading of all risk factors in principal components analysis, albeit it was still substantial. However, this suggests that average performance speeds and consistencies do not appear to differentially relate to the metabolic system perhaps quite as much as simple versus choiceRT tasks might.

Given that the variables loading most highly on the metabolic component, including triglycerides, cholesterol and waist circumference, may reflect excess dietary fat intake and level of sedentary lifestyles, it is perhaps surprising that effect sizes between simpleRT and metabolic risk, particularly in the youngest cohort, were attenuated by about a quarter only, in fully adjusted models that attempted to control for physical fitness and socioeconomic indicators (that co-vary with lifestyle behavioural factors). That significant effects remained, albeit they were small (explaining between 1% and 4% of total variance), leaves open the possibility of alternative explanations to account for these effects.

Strengths

There are several strengths of the present study, most of which echo those of the previous chapter.

First, this study design is novel in testing for the first time the forward association between processing speed and metabolic system risk.

Second, use of less culturally biased reaction time tasks that may be closer in reflecting neuronal integrity relative to IQ performance scores, is a more effective way of testing system integrity theory to explain the cognition-to-metabolic link. Whereas education is often proffered as the confounder in intelligence-health associations, that significant effect sizes were observed for associations between reaction times and cardiometabolic risk suggests that this is an inadequate explanation by itself; education mediated some of the association, but a direct association remained in fully adjusted models.

Third, the follow-up of 20 years between cognitive performance and metabolic system outcome is a considerable time interval and, particularly in the youngest cohort that was 16 years' old at baseline, the likelihood of reverse causation is reduced.

A fourth strength is that the data allowed an investigation of the association within three distinct age cohorts, exposed to different educational and social influences, but which can be compared to one another. Observing different—and in some cases opposing—effect sizes for the association between cognitive performance and metabolic risk is enlightening, not only about the way their transactional relationship may shift with age, but also about the importance of considering sampling bias in the interpretation of findings. Comparing the rates of attrition of the youngest compared to the oldest cohorts (the latter representing one third of the original cohort), of participants recruited at the same time under the same testing conditions, for example, is revealing about how these groups differ in their representativeness. By including a weighting in the model to account for attrition among survivors at wave5, it was possible to reduce this element of bias, which otherwise may have inflated the effect sizes; whereas the previous two studies investigating psychometric intelligence and metabolic syndrome did not account for attrition effects (Batty, Gale, et al., 2008; Richards et al., 2009). However, this weighting did not account for non-survivors, which would have differentially affected the age groups.

Limitations

Interpretation of the present findings must be balanced with the weaknesses of this study design.

First, two out of three of our cohorts were adults at baseline, and therefore significant confounding may have impacted on the effects observed in these two older age groups. However, there is some evidence at least to suggest a lack of differential ageing effects on processing speed throughout the lifecourse; that is, in the Lothian Birth Cohort study, interindividual variances in simple and choice reaction times at age 70 were largely accounted for by individual differences in psychometric intelligence test performance at age 11 (Deary, Johnson, et al., 2010). This may not be the case however for metabolic risk parameters, which may be more differentially affected by lifestyle risk factors and prescription drug treatments, within populations. That the two cohorts were older however revealed differential effects of age on attrition, as has been discussed.

Second, in the absence of data on metabolic risk variables at baseline, interpreting direction of causation between cognition and the metabolic system is more limited. Nevertheless attempts were made to control for confounding and reverse causation at least, by adjusting for baseline covariates. I could not account for diet or alcohol in the present study and how these might explain cognition-to-metabolic risk associations seems an important area for further investigation.

Third, it was necessary to exclude a disproportionate number of women to men from the analysis, particularly in the younger cohorts, due to factors known to influence blood results, such as pregnancy. Therefore results may be weakened by this lack of representation of women.

Finally, multiple testing may have incurred type 1 error in some of the effect sizes observed, as discussed in the previous chapter, and therefore associations where more than one reaction time variable was significantly associated with the metabolic outcome, should be given greater precedence.

Concluding remarks

The association between premorbid cognition and later risk of MetS in adulthood is not limited to higher-level reasoning abilities; that is, similar effect sizes are observed for simpleRT tasks and metabolic risk. Socioeconomic factors and covarying lifestyle behaviours may explain a moderate proportion of the effect; although there is variance left to explain, allowing perhaps for plausibility of underlying system integrity. These findings from the Twenty-07 study highlight the importance of considering cognition-metabolic associations in earlier life, without which, effects reported from cognitive ageing studies may be over inflated and/or wrongly interpreted.

Table 7.1 Adjustments to physiological risk factors according to medication use.

Risk factor	Medication	Adjustment	Reference
Blood pressure	anti-hypertensive	↑ 10mmHg	Tobin, Sheehan, Scurrah, & Burton (2005)
HDL-cholesterol	beta blockers	↑ 10%	Weir & Moser (2000)
HbA1c	diabetic medication	↑ 1%	Kinshuck, Lamb, & Griffiths (2011)

Note. Diabetic medication includes insulin or oral anti-diabetics.

Table 7.2 Descriptive statistics for reaction time variables and covariates, by MetS group.

	1972 cohort			1952 cohort			1932 cohort		
	No MetS	MetS	*p*	No MetS	MetS	*p*	No MetS	MetS	*p*
N (%)	565 (79.5%)	146 (20.5%)		475 (62.7%)	283 (37.3%)		217 (67.6%)	104 (32.4%)	
Age at wave1	15.7 (0.3)	15.7 (0.3)	.859	36.1 (0.7)	36.2 (0.9)	.146	56.3 (0.7)	56.2 (0.6)	.207
Sex									
Men	245 (74.5%)	84 (25.5%)		203 (59.4%)	139 (40.6%)		107 (72.3%)	41 (27.7%)	
Women	320 (83.8%)	62 (16.2%)	**.002**	272 (65.4%)	144 (34.6%)	.088	110 (63.6%)	63 (36.4%)	.096
Wave1 cognition									
SimpleRT m	290 (54)	295 (65)	.399	306 (68)	315 (84)	.199	336 (105)	329 (82)	.782
SimpleRT sd	69 (41)	79 (63)	.099	64 (35)	67 (48)	.507	80 (50)	80 (67)	.491
ChoiceRT m	565 (67)	579 (75)	**.037**	610 (74)	618 (87)	.565	709 (88)	694 (83)	.158
ChoiceRT sd	110 (30)	116 (34)	**.031**	111 (28)	112 (30)	.231	127 (36)	123 (29)	.434
AH4							29.6 (11.7)	31.3 (10.9)	.298
Wave1 covariates									
Current smoker	88 (15.6%)	25 (17.1%)	.648	195 (41.1%)	126 (44.5%)	.350	72 (33.2%)	35 (33.7%)	.933
SES									
Un/partly skilled	73 (13.0%)	27 (18.5%)	**.012**	55 (11.6%)	39 (13.8%)	**.007**	40 (18.4%)	18 (17.3%)	.074
Skilled manual	110 (19.5%)	36 (24.7%)		69 (14.5%)	63 (22.3%)		42 (19.4%)	12 (11.5%)	
Skill non-manual	150 (26.5%)	25 (17.1%)		111 (23.4%)	60 (21.2%)		51 (23.5%)	23 (22.1%)	
Intermediate	162 (28.7%)	50 (34.2%)		167 (35.2%)	90 (31.8%)		72 (33.2%)	39 (37.5%)	
Professional	70 (12.4%)	8 (5.5%)		73 (15.4%)	31 (11.0%)		12 (5.5%)	12 (11.5%)	

WHR	0.85 (0.07)	0.87 (0.07)	**.008**	0.87 (0.08)	0.89 (0.09)	**< .001**	0.86 (0.08)	0.87 (0.08)	.558
Heart rate	72.8 (10.0)	73.1 (10.0)	.744	70.2 (9.5)	71.8 (9.9)	**.022**	70.7 (8.8)	71.6 (9.9)	.408
Education, yrs	14.2 (3.2)	13.3 (3.0)	**.002**	13.0 (3.3)	12.2 (3.0)	**< .001**	10.5 (2.6)	10.8 (3.1)	.262
Wave5 covariates									
SES									
Un/partly skilled	31 (5.5%)	27 (8.9%)	.218	42 (8.9%)	37 (13.0%)	**.002**	52 (24.0%)	18 (17.3%)	.145
Skilled manual	52 (9.2%)	36 (11.6%)		56 (11.8%)	46 (16.3%)		42 (19.4%)	23 (22.1%)	
Skil non-manual	109 (19.3%)	25 (20.5%)		99 (20.8%)	57 (20.1%)		50 (23.0%)	21 (20.2%)	
Intermediate	290 (51.3%)	50 (50.0%)		198 (41.7%)	108 (38.2%)		61 (28.1%)	32 (30.8%)	
Professional	83 (14.7%)	8 (8.9%)		80 (16.8%)	35 (12.4%)		12 (5.5%)	10 (9.6%)	
Current smoker	147 (26.0%)	44 (30.1%)	.317	120 (25.3%)	77 (27.2%)	.555	36 (16.6%)	11 (10.6%)	.154
Heart rate	64.9 (10.1)	70.7 (10.1)	**< .001**	64.8 (10.6)	68.5 (10.8)	**< .001**	64.3 (10.6)	66.7 (11.6)	.063
Contraceptive-use	40 (12.5%)	7 (11.3%)	.322						
HRT-use				28 (10.3%)	13 (9.0%)	.444			

Note. Values are *M* (and *SD*) for continuous variables; *N* (and %) for ordinal variables. HRT = hormone replacement therapy; SES = socioeconomic status; WHR = waist-to-hip ratio.
[a] Independent samples *t*-tests compared 'no MetS' versus 'MetS' groups on continuous variables. Pearson's chi-square compared these groups on categorical variables, including sex, current smoker, contraceptive-use, and HRT-use. ANOVA compared SES groups.

Table 7.3 Odds ratios for (and 95% CI) for MetS risk, predicted by baseline reaction times.

	1972 cohort *N* = 716 to 719				1952 cohort *N* = 748 to 752				1932 cohort *N* = 325 to 326			
	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd
Model 1	0.91 (0.81, 1.03)	**0.79 (0.70, 0.88)**	**0.82 (0.73, 0.93)**	**0.89 (0.79, 1.00)**	0.90 (0.80, 1.02)	0.93 (0.81, 1.05)	0.90 (0.80, 1.02)	0.94 (0.83, 1.06)	1.07 (0.91, 1.25)	1.08 (0.89, 1.32)	**1.49 (1.19, 1.87)**	**1.52 (1.24, 1.86)**
	p = .114	***p* < .001**	***p* = .002**	***p* = .050**	*p* = .097	*p* = .238	*p* = .109	*p* = .337	*p* = .446	*p* = .414	***p* = .001**	***p* < .001**
Model 2	0.95 (0.83, 1.08)	**0.80 (0.71, 0.90)**	**0.87 (0.76, 0.98)**	0.92 (0.82, 1.04)	0.93 (0.82, 1.06)	0.95 (0.83, 1.08)	0.96 (0.84, 1.10)	0.97 (0.86, 1.10)	1.05 (0.88, 1.24)	1.07 (0.88, 1.30)	**1.47 (1.16, 1.87)**	**1.47 (1.20, 1.80)**
	p = .426	***p* < .001**	***p* = .027**	*p* = .169	*p* = .298	*p* = .435	*p* = .544	*p* = .670	*p* = .598	*p* = .512	***p* = .002**	***p* < .001**
Model 3	0.97 (0.85, 1.11)	**0.81 (0.72, 0.91)**	0.90 (0.79, 1.03)	0.96 (0.85, 1.08)	0.94 (0.83, 1.07)	0.95 (0.83, 1.08)	0.97 (0.84, 1.11)	0.98 (0.86, 1.11)	1.04 (0.88, 1.24)	1.07 (0.88, 1.30)	**1.46 (1.15, 1.87)**	**1.46 (1.19, 1.80)**
	p = .695	***p* < .001**	*p* = .120	*p* = .494	*p* = .362	*p* = .411	*p* = .606	*p* = .702	*p* = .623	*p* = .520	***p* = .002**	***p* < .001**
Model 4	0.99 (0.86, 1.14)	**0.79 (0.71, 0.89)**	0.91 (0.79, 1.04)	0.94 (0.83, 1.07)	0.95 (0.83, 1.08)	0.95 (0.83, 1.08)	0.97 (0.85, 1.11)	0.98 (0.87, 1.12)	1.07 (0.90, 1.27)	1.09 (0.89, 1.33)	**1.44 (1.13, 1.84)**	**1.43 (1.17, 1.76)**
	p = .888	***p* = .007**	*p* = .177	*p* = .328	*p* = .400	*p* = .414	*p* = .688	*p* = .808	*p* = .453	*p* = .413	***p* = .003**	***p* = .001**

Note. Values are odds ratios (and their 95% confidence intervals); those in bold are statistically significant ($p < .05$). All models include an inverse probability weighting to account for attrition bias. Reaction time variable scores were reversed, so that lower values indicate slower and more variable performance. Model 1 is adjusts for sex, age at wave1, and wave5 dummy variables (oral contraceptive use in 1972 cohort; HRT use in 1952 cohort); Model 2: Model 1 + baseline CVD covariates; Model 3: Model 2 + education; Model 4: Model 3 + wave5 CVD covariates (excl. WHR). CVD covariates are current smoking, occupational status, heart rate, waist-to-hip ratio; *m* = mean RT speed; *sd* = RT standard deviation. There were no issues of multicollinearity.

Table 7.4 Principal components analysis of 5 metabolic risk variables.

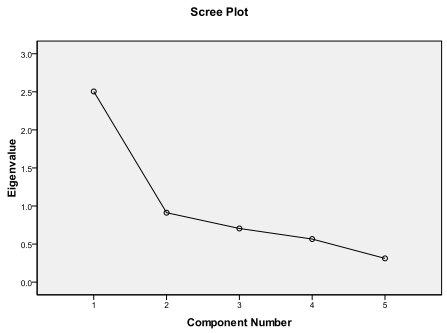
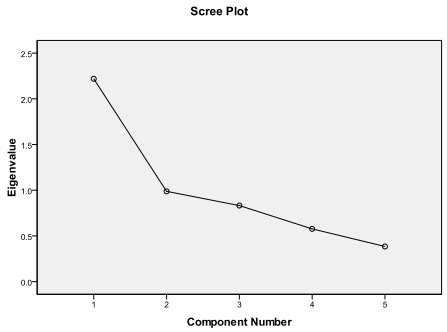
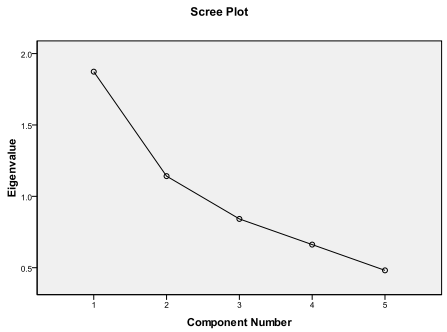
Birth cohort	Component	Loading	Scree
1972			
KMO = .73 Bartlett's, $p < .001$ 50.1% variance explained	Triglycerides LDL cholesterol Waist circum HDL cholesterol HbA1c	.85 .77 .74 -.68 .42	
1952			
KMO = .60 Bartlett's, $p < .001$ 44.4% variance explained	Triglycerides HDL cholesterol Waist circum LDL cholesterol HbA1c	.82 -.75 .65 .61 .45	
1932			
KMO = .60 Bartlett's, $p < .001$ 37.5% variance explained	Triglycerides HDL cholesterol Waist circum HbA1c LDL cholesterol	.76 -.70 .62 .47 .46	

Table 7.5 Regression coefficients (and 95% CI) for associations between baseline reaction times and the metabolic component after 20 years.

	1972 cohort *N* = 700 to 703				1952 cohort *N* = 750 to 754				1932 cohort *N* = 325 to 326			
	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd
Model 1	**.198 (.149, .248)**	**.337 (.295, .379)**	**.156 (.102, .210)**	**.127 (.076, .177)**	**.087 (.015, .158)**	**.096 (.021, .171)**	**.078 (.006, .150)**	.005 (-.065, .076)	-.019 (-.008, .070)	-.022 (-.128, .085)	-.039 (-.159, .081)	-.069 (-.170, .032)
	***p* < .001**	***p* < .001**	***p* < .001**	***p* < .001**	***p* = .017**	***p* = .012**	***p* = .035**	*p* = .882	*p* = .674	*p* = .691	*p* = .525	*p* = .180
Model 2	**.133 (.082, .183)**	**.311 (.269, .353)**	**.065 (.011 .119)**	**.061 (.011, .111)**	.055 (-.015, .126)	.067 (-.006, .141)	.025 (-.049, .098)	-.031 (-.100, .038)	-.041 (-.134, .051)	-.027 (-.133, .079)	-.073 (-.201, .056)	-.075 (-.175, .026)
	***p* < .001**	***p* < .001**	***p* = .018**	***p* = .018**	*p* = .125	*p* = .072	*p* = .514	*p* = .374	*p* = .382	*p* = .621	*p* = .267	*p* = .144
Model 3	**.130 (.080, .181)**	**.311 (.268, .354)**	**.060 (.005, .115)**	**.055 (.004, .107)**	.052 (-.019, .123)	.069 (-.004, .143)	.022 (-.052, .096)	-.032 (-.101, .037)	-.040 (-.133, .052)	-.026 (-.133, .080)	-.071 (-.200, .058)	-.073 (-.174, .028)
	***p* < .001**	***p* < .001**	***p* = .032**	***p* = .034**	*p* = .154	*p* = .064	*p* = .562	*p* = .359	*p* = .392	*p* = .625	*p* = .282	*p* = .154
Model 4	**.088 (.037, .139)**	**.297 (.254, .339)**	.035 (-.019, .089)	.049 (-.001, .099)	.051 (-.020, .122)	.069 (-.004, .142)	.021 (-.053, .095)	-.036 (-.105, .033)	-.048 (-.142, .045)	-.029 (-.136, .077)	-.062 (-.192, .067)	-.065 (-.166, .036)
	***p* = .001**	***p* < .001**	*p* = .203	*p* = .056	*p* = .159	*p* = .064	*p* = .581	*p* = .302	*p* = .308	*p* = .588	*p* = .346	*p* = .207

Note. Values are unstandardised regression coefficients (and 95% CI). Those in bold font are significant ($p < .05$). Higher RT values are slower (m) and more variable (sd). All models are weighted for attrition. CVD covariates = smoking, occupational status, heart rate, waist-to-hip ratio.
Model 1 adjusts for sex, age at wave1, and wave5 dummy variables (oral contraceptive use in 1972 cohort; HRT use in 1952 cohort)
Model 2: Model 1 + baseline CVD covariates
Model 3: Model 2 + education
Model 4: Model 3 + wave5 CVD covariates (excl. WHR)

Table 7.6 Regression coefficients (and 95% CI) for contemporaneous associations between reaction times and the metabolic component.

	SimpleRT m	SimpleRT sd	ChoiceRT m	ChoiceRT sd
1972 cohort	*N* = 703			
Model1	.001 [-.005, .007] *p* = .726	.013 [-.005, .031] *p* = .145	**.007 [.003, .011]** ***p* < .001**	**.015 [.006, .023]** ***p* = .001**
Model2	-.003 [-.008, .003] *p* = .352	.010 [-.008, .028] *p* = .267	**.004 [.000, .007]** ***p* = .039**	**.010 [.002, .018]** ***p* = .019**
1952 cohort	*N* = 746			
Model1	**.007 [.001, .014]** ***p* = .018**	.014 [-.005, .033] *p* = .139	**.007 [.003, .012]** ***p* < .001**	**.014 [.004, .023]** ***p* = .004**
Model2	.005 [-.001, .011] *p* = .076	.010 [-.008, .028] *p* = .273	**.005 [.002, .009]** ***p* = .004**	**.014 [.005, .022]** ***p* = .002**
1932 cohort	*N* = 479			
Model1	.002 [-.012, .015] *p* = .794	-.006 [-.041, .029] *p* = .726	-.002 [-.011, .007] *p* = .646	-.009 [-.030, .013] *p* = .426
Model2	.001 [-.012, .015] *p* = .785	-.002 [-.037, .032] *p* = .918	-.001 [-.009, .007] *p* = .857	-.008 [-.029, .012] *p* = .465

Note. All models include the inverse probability weight for attrition. Model1 and Model 2 match on sample sizes for each association. The regression coefficient is the effect of a one point change in the metabolic component (independent) variable in relation to a log-transformed unit change in the RT (dependent) variable; those in bold are statistically significant ($p < .05$). Model 1 adjusts for age at wave5, sex, and dummy variables at wave5 (oral contraceptive among 1972 cohort; HRT among 1952 cohort); Model 2 is model1 + corresponding wave1 RT variable.

Chapter 8
General Discussion

The thesis investigated the extent to which social and behavioural variables explain the variance in mortality or morbidity risk as predicted by premorbid cognitive ability. Meta-analysis that aggregated effect sizes of 16 longitudinal studies of baseline psychometric intelligence and total mortality-risk assessed confounding by parental socioeconomic status and mediation by education and adult social class. The study also considered potential sex differences. The close phenotypic association between education and intelligence variables was tested for heritability in two national cohorts of schoolchildren, raising the issue of overadjusted models in cognitive epidemiology. Further large and well-characterised longitudinal cohort studies were used to assess social and behavioural mediation in pathways from cognitive performance to cardiovascular disease (CVD) risk factors. In two of these, reaction times were used as alternatives to psychometric test scores, thereby reducing cultural bias in measuring premorbid cognition.

Summary of findings

IQ and all-cause mortality

The first meta-analysis of individual differences in premorbid intelligence and adult mortality risk was completed (Chapter 2), which investigated the following: 1) The aggregate effect size of the unadjusted association between intelligence in youth and all-cause mortality risk; 2) Cohort-specific effects, including by age and sex; 3) Confounding by early life factors, including socioeconomic background; 4) Mediation explained by either adult occupation or educational attainment. The results reported a significant inverse association between psychometric intelligence in youth and mortality risk by follow-up validating the report of a previous systematic review on a smaller number of studies (Batty, Deary, Gottfredson, 2007); that is, a one *SD* advantage in intelligence test performance

related to the 24% reduced hazard of death by follow-up. The aggregate effect sizes relating an advantage in intelligence test performance to lower risk of premature mortality were equivalent for men and women, despite three individual studies reporting sex differences. Although it was recognised that sex differentials are important factors for consideration in cognitive epidemiology, particularly given distinct patterns of disease risk prevalence between men and women, these few studies also reported: 1) Cohort-specific effects, for example, a disproportionate loss of men with above average intelligence to war, or, 2) Low cases of mortality among women. In studies that adjusted for background socioeconomic status (predominantly using parental occupational as the control variable), there was negligible change to the IQ-mortality effect size. This was also true of the few studies that further controlled for birth weight and gestational age. The interpretation of this finding was that the relation of cognitive ability to mortality risk is independent of early life social inequality and/or birth effects, and therefore confounding is an unlikely explanation.

Findings from studies that controlled for either occupational status in adulthood, or educational attainments however, demonstrated that the IQ-mortality link was significantly and partially attenuated. This was understood to support the idea of a forward association from cognitive reasoning ability to mortality risk that is mediated via these socioeconomic achievements and influences. However, the interpretation of a stronger attenuation effect by education, relative to occupation, held the caveat that overadjustment may have arisen by using a control variable that shares strong phenotypic covariance with intelligence performance. I observed a low degree of heterogeneity across the included studies' effect sizes. However, cohorts followed up for longer—which also tended to be the youngest tested for intelligence—showed smaller effect sizes than those where mortality records were traced after shorter follow up. There is no single clear interpretation of this, although I proposed that 'time to mortality' would be determined by 'cause of mortality' that is likely differentially related to baseline intelligence.

Intelligence and education: Nature of association

The behaviour genetics studies, using a novel whole-population indirect twin design applied to two European cohorts of elementary schoolchildren (Chapter 3 and Chapter 4), replicated high genetic covariance estimates of the association between psychometric intelligence scores and academic attainments. These were generally at the high end of estimates reported from the background literature, in which twin studies that depend on self-selection may incur bias. The findings highlight the difficulty of adjusting for education variables in models that include intelligence test scores; that is, if performance on academic achievement tasks and IQ-type tests are strongly associated, and that association is due to shared underlying genetic influence, then controlling for education in cognitive epidemiological models may result in some overadjustment. The finding in the UK cohort, that verbal as well as nonverbal reasoning tasks showed equivalent genetic covariance estimates with academic attainment (Chapter 3), was considered to support a theory that a general and heritable cognitive trait drives associations with academic skills, rather than educational experience causing variance in IQ-test performance, through the development of language skills for example. I did not replicate the previously reported increase in genetic covariance with age in the Dutch cohort comparing estimates of 8 and 12 year-old schoolchildren (Chapter 4); the unexplained drop in the heritability of the 10 year-old group may suggest specific age- and/or time-effects of shared environmental influences; unless this was due solely to large standard error.

Cognition and preclinical CVD

Release of biomedical survey data from the 1958 National Child Development Study, allowed for the first investigation in the literature on associations between childhood psychometric intelligence scores and midlife systemic inflammation and haemostasis (Chapter 5), measured 34 years apart. In this large population-representative cohort, an advantage in premorbid cognition was significantly associated with lower levels of inflammatory biomarkers including CRP and fibrinogen, thus replicating results from a study of older adults. Furthermore, although effect sizes were relatively smaller, higher premorbid ability also

significantly related to lower levels of the haemostatic biomarkers, D-dimer, t-PA antigen, and VWF antigen. These latter findings are a novel aspect of the study and, I suggest, they highlight the potential for multiple mechanisms linking behavioural cognition to biological disease risk. Confounding by birth status and socioeconomic background explained only a minor proportion of these effects; the associations were better explained by a forward association, mediated via multiple lifestyle indicators, including smoking, abdominal obesity and occupational status. Nevertheless, cognitive reasoning ability in youth and systemic inflammation were still related even after accounting for all study covariates. Inferred from this was the possibility of underlying system integrity explaining indirect associations among behavioural and biological variables; that is, on the condition that reverse causation was ruled out. A weakness of this study was the absence of biomedical data at baseline that would have tested reverse causation. The study design did however allow for its testing in the forward association from midlife inflammation, to cognition five years later. The finding that baseline intelligence explained most of these effects in middle age highlights the need to consider the possibility of (1) Underlying system integrity explaining lifetime cognition-inflammation associations; (2) Bidirectional associations between behavioural cognition and inflammatory status influenced by environmental effects in early stages of adulthood.

The final chapters make contributions to the cognitive epidemiological literature by reporting on cognitive processing speed in relation to CVD risk factors—whereas results from the background literature depend largely upon psychometric IQ-type test performance in relation to CVD risk. The novelty of the west of Scotland Twenty-07 study cohort also allowed for the possibility of assessing longitudinal effects in three age groups. The first study replicated the forward association between higher premorbid cognition (at age 16) and lower systemic inflammation as reported in Chapter 5, and this time measured after 20 year follow up (Chapter 6). The effects which were significant in men for two out of four reaction time variables (choice speed and consistency), were largely attenuated after control for baseline and follow up covariates, and I observed smoking to be a significant factor. However, in women lifestyle influences did not explain the significant effect of more consistent simple reaction time in relation to CRP, which

persisted as a direct effect. Faster and more consistent processing speeds among 36 year-old men— an age when confounding was an increased possibility—related to lower fibrinogen 20 years later. Whereas two of these three effects were no longer significant after accounting for baseline smoking and occupational status, simple reaction time speed was not explained by either confounding or mediating factors. This latter finding leaves open the possibility that system integrity may explain an indirect association between low-level cognitive performance and blood status that relates to CVD risk. Unexpected reverse findings from the older cohort, 76 years' old by follow up, were attributed to attrition and survival bias. In the follow up wave of testing, significant contemporaneous associations between systemic inflammation and reaction time speed and variability in the 1952 cohort, were not accounted for by equivalently-measured processing speeds at baseline. Therefore I suggested that, either cognitive processing speed is differentially affected by inflammatory status in middle-age, or lifestyle behaviours in the second and third decades of adulthood underlie indirect associations between these parameters measured in midlife.

In the final empirical chapter processing speed in youth was associated with metabolic syndrome biomarkers 20 years later, replicating effect sizes of two previous studies that reported on psychometric intelligence in relation to this premorbid CVD condition (Chapter 7). The effects were more robust when I modelled metabolic syndrome risk as a continuous rather than dichotomous measure; that is, simple reaction time speed and variability at age 16 held direct associations with a metabolic-risk component score in fully-adjusted models that accounted for education, socioeconomic status, smoking, and an indicator of physical fitness. I suggested that the possibility of underlying system integrity explaining this cognition-metabolic association remains open. Although faster and more consistent reaction times at age 36 predicted a metabolic syndrome component score 20 years later, this did not survive adjustment for potential confounding effects. That simpleRT but not choiceRT performance in youth held associations with later metabolic risk, while choiceRT but not simpleRT performance at ages 36 and 56 held contemporaneous associations with metabolic risk, implied that simple RT tasks may have greater utility for the empirical testing of system integrity in cognitive epidemiology.

Contributions to the literature

The role of education in cognitive epidemiology

A major theme of this thesis was to consider the role of education in pathways from premorbid intelligence to CVD risk factors or all-cause mortality in adulthood. The meta-analysis of Chapter 2 found that adjusting for education in the association between intelligence and total mortality reduced the effect by about half while it retained statistical significance. This study therefore contributes to the literature (Calvin, Deary, et al., 2011) in showing independent effects of intelligence differences on mortality risk after considering education, whereas cognitive influences in epidemiology and health psychology have sometimes been overlooked, considered mere proxies for social inequalities related to health (Lubinski, 2009; Lubinski & Humphreys, 1997).

Nevertheless the partial attenuation effect by education is also an important finding, and is the most consistent and substantial reported in cognitive epidemiology, and relevant to studies that predict a diverse range of health outcomes (as outlined in Chapter 1). Given that inclusion criteria for the meta-analysis required that cognitive ability be measured in youth as an indicator of premorbid intelligence, and, with the knowledge that individual differences in childhood intelligence remain highly stable throughout adult life (Deary et al., 2000), mediation was the likely role of education in this pathway. That is, higher cognitive performance leads to greater success in academic tests (Deary et al., 2007), spending longer in learning establishments, and, finally achieving higher educational qualifications; and through these experiences a healthier and longer lifespan is ensured. A proposed mechanism is that education reinforces health literacy and engagement with public health messages, thereby affecting personal health risk assessment, behaviour and management (Torssander & Erikson, 2009).

However, there is the possibility that education is also a partial confounder in IQ-mortality pathways, particularly given that half the studies in the meta-analysis

tested cognitive ability beyond the age of compulsory school education. Therefore, educational fulfilment took temporal precedence to the intelligence performance measure, thus increasing the chance of reverse causation between these two measures (Bhopal, 2008) and confounding of the intelligence-mortality effect.

A cautionary tale

The potential for bidirectional associations between academic and intelligence test performance is accepted in cognitive epidemiology (Deary & Johnson, 2010; Richards & Sacker, 2011), particularly with recent evidence that time spent in education can affect intelligence test performance in later youth (Brinch & Galloway, 2012), just as studies previously accumulated that IQ tests predicted educational outcomes. This thesis therefore raises the importance of interpreting findings in relation to mediation or confounding with sensitivity to cohort age at different waves of follow-up, and the temporal positioning of education and cognitive variables.

Although mainly cross-sectional associations between academic achievement and intelligence tests were the subject of Chapters 3 and 4, the need for age- and time-sensitivity in interpreting their association was highlighted by the age-differential effects in the Dutch cohort, a transient period at age 10 where seemingly persistent high genetic covariance between traits in childhood was replaced by strong shared environment effects (albeit with large standard errors).

Within this age range at elementary school there was also an indication among British schoolchildren that an underlying trait for intelligence drove the high genetic covariance with academic achievement, given that different domains of cognitive ability were similar in the magnitude of their genetic association with the educational component. If on the other hand attained knowledge had caused individual differences in intelligence test scores at this age, one might have expected stronger shared environmental associations between academic performance and verbal reasoning skills, relative to nonverbal reasoning skills, for example. This was not evident.

The observations from the behaviour genetics analysis of this thesis should be heeded in cognitive epidemiology. That is, when cognitive and educational measures are assessed, in childhood at least, their strong association will more often than not, be largely driven by genetic effects, and therefore including both variables as predictors in pathway models may lead to statistical overadjustment. One interpretation of the high genetic overlap between these two tests is that, at this age at least, academic and intelligence tests are more proxy measures of each other than assessments of independent abilities. However, recent factor analysis of individually-administered academic and intelligence test scores throughout childhood show that these extensive data consistently result in two distinct and separate constructs, of acquired knowledge and general reasoning ability respectively (Kaufman, Reynolds, Liu, Kaufman, & McGrew, 2012).

On reducing risk of overadjusted models

The independent effect of cognitive ability on health outcomes, on accounting for educational influence, was reinforced in Chapters 6 and 7 where faster and more consistent reaction time performance in youth were associated with reduced inflammation and metabolic syndrome risk in adulthood, after controlling for education, which has also been related to these outcomes (Gimeno, Ferrie, et al., 2008; Langenberg et al., 2006). The risk of overadjustment by education would have been minimised due to lower correlations between processing speeds and education, relative to those for psychometric intelligence and education, as well as performance on these tests carrying low cultural bias.

The effects of processing speed on later inflammatory and metabolic risk make novel additions to the literature, which has largely focused on the reverse temporal ordering of these variables. Furthermore, given reports from large and well-characterised cohort studies that education entirely mediates the association between psychometric intelligence and metabolic syndrome (Richards et al., 2009), obesity (Chandola et al., 2006), and coronary heart disease (Lawlor et al., 2008), the study reported in Chapter 7 challenges how generalisable these findings might be. Although the behavioural risk factors for metabolic syndrome are likely mediated via

educational and social experiences, there exists the possibility that direct effects persist between intelligence and later health risk, which may find root in system integrity and/or early life influence. Such influences are addressed in sections below.

Beyond socioeconomic influence

The potential for socioeconomic status to confound or mediate intelligence-health risk pathways was investigated in four chapters of this thesis, by controlling for parental occupation and study member's occupation respectively.

Differential effects of confounding

In Chapter 2, early life socioeconomic status—which as well as indicating financial resources, may be a partial proxy indicator for heritable intelligence and parental health status—contributed negligible variance in mortality risk explained by intelligence differences across nine studies. In the association between childhood intelligence and midlife inflammation reported in Chapter 5, SES at birth explained from a quarter to almost a half. Along with smoking status at baseline, SES attenuated effects of faster and more consistent choice reaction times and lower inflammation by about two thirds (Chapter 6), and its unique contribution was about a third. Similar attenuation effects by parental occupation were also observed in Chapter 7, particularly for associations between premorbid choice reaction times and metabolic syndrome risk; significant associations between simple reaction time measures and metabolic risk were attenuated by baseline social status, but to a lesser degree.

It is therefore difficult to generalise from these findings as to the extent to which background socioeconomic influences confound associations in cognitive epidemiology. It could be argued that cognitive and social variables that are measured more proximally to one another (e.g. Chapters 6 and 7) will carry stronger associations, relative to those that are temporally distant (Chapter 5), thus contributing to different degrees of attenuation. An alternative explanation is that SES may be a greater confounder in effects of reaction time on health outcomes,

relative to psychometric intelligence, given that early life social inequalities relate to individual differences in neural development (Hackman, Farah, & Meaney, 2010), which processing speeds may better reflect. Nevertheless, that I did not find baseline or antecedent parental socioeconomic status to fully account for the effects of cognition on health outcomes again highlights the important role of human trait individual differences in epidemiology beyond social inequalities, which Lubinski and Humphreys (1997) have advocated.

Mediation by social attainment

Socioeconomic status was also found to be a partial mediator of cognition-to-health risk associations in this thesis. Occupational status of study members in adulthood explained a third of the IQ-mortality aggregate effect (Chapter 2); it explained over half of associations between childhood intelligence and midlife inflammatory and haemostatic biomarkers (Chapter 5); and in associations between choice reaction times in youth and a metabolic syndrome component 20 years later (Chapter 7), SES and covariates mediated the effects to non-significance. However, work occupations in adulthood explained to a far lesser extent the association between simple reaction times in youth and later metabolic risk, in this final empirical chapter, and made little dent to the effect sizes from Chapter 6, which related simple reaction times to later systemic inflammation, although many of these effects had already been fully accounted for by baseline-adjusted models.

It is possible therefore, that choice reaction times, which are more strongly related to intelligence test performance compared to simpleRT (Deary, Der, & Ford, 2001), may be mediated by social inequalities to a larger extent in their relation to health outcomes, than their more basic counterparts. These are among the first studies to test these associations among socioeconomic status, processing speeds and CVD biomarkers however; therefore interpretations remain tenuous until findings may be replicated.

Mediation by health behaviours

The kinds of health behaviours tested for mediation (and confounding) in cognitive epidemiology will be determined by their role as risk factors for specific morbidities. It was therefore not possible to assess aggregate effects of behavioural mediation in the meta-analysis, given the heterogeneous range of covariates in individual studies predicting all-cause mortality. The health behaviours that are risk factors for CVD—a specific outcome of interest in this thesis—include smoking, physical non-activity (or sedentary lifestyle), diet that includes high saturated fat and total cholesterol intake, and excess alcohol consumption. The majority of these were considered in pathways from cognition to inflammation, haemostasis, and metabolic risk respectively, in the second half of this thesis.

Smoking

I observed substantial mediation by smoking in the associations between premorbid cognition and adult inflammatory status in the two studies from Chapters 5 and 6. In the 1958 National Child Development Study, current smoking status, tested as a mediating covariate at age 42 years, attenuated by over half the association between age 11 psychometric intelligence and age 46 systemic inflammation. In the Twenty-07 study baseline smoking alone attenuated by a third-to-half the associations between age 16 choice reaction times (speed and variability) and age 36 systemic inflammation; although as analyses in Chapter 6 were by sex group, this effect of smoking was restricted to men. I suggested that the sex differential effect of smoking on inflammatory status (Onat et al., 2008; The Fibrinogen Studies Collaboration, 2007) might explain this. Although in this latter study smoking was assessed at the same time as baseline cognition, it was supposed that the effects of smoking on the cognition-inflammation association was more likely due to mediation than confounding; for one, smoking in childhood (in the short-term) was unlikely to have caused adverse changes to processing speed. These attenuation effects by smoking are strong, relative to studies reporting more modest attenuation effects in associations between intelligence differences and later all-cause mortality (Batty, Shipley, Mortensen, Boyle, et al. 2008; Jokela, Batty et al., 2009), and are therefore revealing about the specific mechanistic pathways that lead from

cognition through excess circulatory inflammation to specific CVD morbidities, although such pathways still require formal testing. It has already been reported that cognitive reasoning ability is predictive of smoking; that is, those with higher reasoning abilities are relatively infrequent cigarette smokers (Batty, Deary et al., 2007b; Batty, Deary et al., 2007c; Taylor et al., 2003). However, this is the first report to show that smoking is a significant mediator in cognition-to-inflammation pathways; a consistent finding whether premorbid cognition is measured by psychometric or experimental testing.

On the other hand, the pathway from cognition to metabolic syndrome risk was not explained by smoking status, in Chapter 7. Smoking, along with other health behaviour indicators including heart rate and waist-to-hip ratio, were controlled for at baseline to account for confounding and/or reverse causation, but these did not explain the significant associations observed. Neither did smoking or heart rate (a proxy measure for physical activity) suggest mediating effects from cognition to metabolic syndrome risk in the Twenty-07 cohort. Only socioeconomic status partially attenuated the effect at baseline and follow-up respectively. The variance in the effect of occupational status may conceal other health behaviours—such as dietary factors and/or alcohol consumption—that could provide a more accurate picture of mediation pathways, and it is suggested that these be included in future studies.

Indirect evidence for system integrity

System integrity theory was introduced by Whalley and Deary (2001), as an explanation (not necessarily an exclusive one) for observations between cognitive traits and health outcomes. Yet the search for an elusive underlying biological trait remains a challenging proposition. There may be direct means to test system integrity via exploratory molecular genetics research. Perhaps more convenient, by use of easily accessible data, are the indirect approaches adopted in this thesis.

First, if associations between premorbid intelligence and disease-risk or mortality could not be fully explained by all potential confounding and mediating variables, and that reverse causation was unlikely, then system integrity remains a

possible explanation. I found evidence to support this from several empirical chapters of this thesis (Chapters 2, 5, 6, and 7). For example, in the 1958 National Child Development Study childhood intelligence was significantly inversely associated with adult systemic inflammation in fully-adjusted models; in the Twenty-07 cohort simple reaction time (but not choiceRT) measures retained significant associations (in some cases) with later inflammatory biomarkers and a metabolic component, again in fully-adjusted models. In light of this observation I proposed in Chapter 7 that simple reaction time might be a more reliable indicator of a latent trait for system integrity than choice reaction time—the latter being more effective in measuring lifetime insult-related neurological changes in human ageing studies.

Second, several indicators of system integrity have been proposed (Gale, Batty, et al., 2009), and one of these, tested here, was cognitive reaction time—although before this thesis, its forward association with later health outcomes had only been investigated in adult-aged cohorts (Deary & Der, 2005; Shipley et al., 2006), and may therefore have been subject to attrition bias, ageing-effects, and/or morbidity-related effects, as suggested for the older age cohort of the Twenty-07 study. Chapters 6 and 7 considered the plausibility of this low-level cognitive indicator of a latent system integrity trait, measured in youth, to predict disease biomarkers at extended follow-up to adulthood. Both studies found equivalent effect sizes to those where psychometric intelligence in youth has been the predictor. Unfortunately the Twenty-07 study does not have intelligence test scores from youth that might have tested system integrity more robustly; that is, to test whether simple reaction time performance (the intermediate phenotype) would fully account for associations between psychometric intelligence and metabolic syndrome risk. Nevertheless, as processing speed is considered to be intermediate of neuronal integrity and higher-level cognitive reasoning capabilities (Deary, Bastin, et al., 2006), to find significant associations between processing speed measures and biomarkers is to step closer to a system integrity proposition in cognitive epidemiology.

That direct associations were observed between cognitive processing speed and continuous measures of inflammation and metabolic function is compatible with the concept of allostasis, a neurobiological process where there are "…bidirectional

patterns of communication between the brain and the autonomic, cardiovascular, and immune systems via neural and endocrine mechanisms" (McEwan & Gianaros, 2010, p. 190). That these existed after accounting for social and behavioural stressors in adulthood, suggests that some of the observations reported in cognitive epidemiology may have a biological underpinning, either explained by system integrity (realised at conception) or environmental stressors in earlier life, or perhaps an interaction of the two (to be explored in future epigenetic research).

Methodological considerations

Confounding

A major issue in all epidemiological research is the elusive confounding variable or set of variables left unaccounted for in analysis of longitudinal data. I addressed this in several of the empirical chapters of this thesis (Chapter 2, 5, 6, and 7), by statistical control of birth weight and gestation, socioeconomic status in early life, smoking, heart rate, and/or waist-to-hip ratio. Many of these were collected at baseline, contemporaneous with premorbid cognitive measures, when potential confounding effects could be inferred at best. However, there remains a need in this field to consider events of childhood or earlier, which could account for indirect associations between cognition and health. System integrity may be the most antecedent of confounders, implying a genetic basis determined at conception. There are however, early life exposures in utero, at birth, and postnatally, that could hold the key to understanding these later adult associations (Thompson et al., 2010), influencing both neurodevelopment and subsequent cognition, and, the susceptibility of later life chronic disease (Gluckman, Hanson, Cooper, & Thornburg, 2008). Such exposures include nutritional status, maternal stress, maternal disease or infection, and/or impacts of adverse psychosocial experience. Longitudinal studies that begin selection in the antenatal period of life would be the ideal study design in which to investigate these factors (Thompson et al., 2010 include a list of such cohorts), as long as the resources exist to then follow up these individuals throughout their lifespan, or at least link them to later adult morbidity records. However, no one study

design offers the ideal blueprint to test all confounders, unless personnel and financial resources, and participant compliance, are unlimited. Collective evidence that addresses the plausibility of confounding between variables is therefore useful—as in the study of education's role in cognitive epidemiology—and various methodologies may contribute to this evidence; for example, behaviour genetics studies as in Chapters 3 and 4.

Reverse causation

The potential for reverse causation is a related issue to confounding, in the empirical studies of this thesis. Although it was possible to test for reverse causation of the forward association between disease biomarkers (inflammation and haemostasis in Chapters 4 and 6, and metabolic risk in Chapter 7) and cognition, by adjusting for earlier cognitive performance, it could not test it in the opposite direction. That is, biomarker data were not available at baseline or earlier, to control and test whether a forward association between cognition and biological risk (as interpreted from the temporal ordering of these variables) remained robust. Ideally such biomarkers would be tested at the earliest ages possible, in the kind of study design proposed to also test for confounding. However it is noted that variances in many biomarkers are limited in childhood.

Chance findings

There is also the possibility that large cohort studies yield greater numbers of false positive findings, and which have very little utility for policy or practise translation (Thompson et al., 2010). At least replication studies provide the confidence that findings are not merely products of chance alone, as I showed in the meta-analysis of this thesis. Although the twice observation that higher premorbid intelligence predicted lower risk of later metabolic syndrome was replicated using an experimental cognitive measure in Chapter 7, it remains to be seen whether future studies using processing speeds would find the robust relationships to specific disease biomarkers, that have been observed using psychometric testing.

Future directions and recommendations

The field of cognitive epidemiology already lays claim to a significant body of empirical work, although it began in earnest about a decade ago (Batty & Deary, 2004; Whalley & Deary, 2001) or more (O'Toole et al., 1988). In testing out the various theories as to why higher premorbid intelligence test scores should confer protection from premature mortality in adulthood (Deary, 2008), pre-existing longitudinal cohorts have largely been used, with progress in testing some theories more than others; for example, the role of lifetime social and behavioural factors that help explain the association. My thesis predominantly contributes to this latter interest. The work in earlier sections validated some key findings in the field, such as the lesser role of early socioeconomic status in explaining the IQ to all-cause mortality association, but partial mediation via educational opportunity and socioeconomic attainment. Furthermore, it reported on novel empirical work investigating mechanisms of association between premorbid cognition and later preclinical stages of CVD—specifically inflammation and metabolic syndrome—identifying significant contributions from social inequalities (common to all outcomes) and smoking (specific to inflammation). As well as exploring social and behavioural influences however, the latter empirical chapters also reported unexplained variance. The various theories linking intelligence to health outcomes require further consolidation however, and some in particular (e.g. system integrity and early life confounding) require greater research investment before they can be properly tested.

Further testing of integrity biomarkers

Given evidence of significant associations between processing speed performance and brain imaging biomarkers, and that reaction times measured in youth predicted adult CVD biomarkers in this thesis, it is recommended that future longitudinal cohort studies consider further use of reaction time tasks (within a

premorbid age range), among other potential indicators of an underlying system integrity trait, for testing in cognitive epidemiology. Alternative measures were described in Chapter 1, and include the stress hormone cortisol, and indicators of physical fitness. This endeavour may be particularly relevant to models predicting CVD morbidities, where there exists biological plausibility for system integrity to underlie cognitive and vascular processes. Furthermore, the two putative biomarkers of disease related to reaction times in this thesis—inflammation and metabolic syndrome component—belong to a wider network of biomarkers that comprise allostasis (Juster et al., 2010). To investigate premorbid cognition in relation to an allostatic indicator—each measured ideally at various time points over the lifecourse—would further enlighten directions of association between cognitive performance and adult health status. This would involve collection of more extensive biomarker data, including stress hormones and alternative inflammatory measures (e.g. interleukin-6), which would potentially capture greater accuracy in disease risk-burden from both genetic and environmental exposures. Such work would contribute not only to theoretical understanding in cognitive epidemiology but to scientific understanding of cognitive and biological exchanges in ageing processes, with ultimate translation to health policy.

Understanding specific mechanisms of health behaviour

As reported in this thesis however, there are likely to be multiple mechanisms by which premorbid intelligence relates to later mortality, varying in their strength according to the specificity of disease or cause-related death. To take childhood cognition and later CVD-risk as the example from this thesis, there are social, behavioural, and likely biological contributions to this pathway, based on the data presented, with varying degrees of their influence depending on subtype of CVD.

If lower intelligence performance in youth is partially predictive of excessive inflammatory status in later life because of the increased likelihood of smoking, then it is of public interest to understand the differential effects of cognition on taking up and persisting in this adverse health behaviour. Government policy in democratic societies may only do so much—by restricting the convenience of smoking in public

and regulating marketing policy—to reduce its burden on public health care and expenditure. As socioeconomic indicators often mediate the association between psychometric intelligence and smoking status (Modig & Bergman, 2012), it remains to be seen whether this is an effect of confounding and/or mediation.

Furthermore, the finding in this thesis that smoking mediated the effect of reaction times on inflammation in men, but not women, is interesting and novel. Although the meta-analysis found no sex difference in IQ-total mortality effect sizes, sex effects should continue to be assessed, given the distinct behavioural and biological profiles of men and women as well as patterns of disease risk over time. Among the other lifestyle factors that the World Health Organisation (http://www.who.int) identifies as increasing CVD prevalence among urbanised, industrialised and globalised nations, are sedentary living and unhealthy diets. These behaviours could be considered more rigorously in future studies, if all environmental influences are to be accounted for in associations between cognition and CVD risk.

A call to social epidemiology

The successful application of robust epidemiological practices to large well-characterised cohorts gives considerable validity to findings, and sets a high standard for continuing work in cognitive epidemiology. This should bring individual differences in intelligence—and with it, other psychological traits including personality and mood—to the attention of epidemiologists who share an interest in understanding pathways of influence to health inequalities, and who link with policy makers to affect change. It may still be common practice to put socioeconomic influences before intelligence differences in mapping out causal factors of disease in social epidemiology (Gallo et al., 2009; Marmot, 2010; Marmot & Kivimäki, 2009)—indeed some continue to ignore the role of psychological traits altogether (Cullen, Cummins, & Fuchs, 2012)—yet there remains compelling evidence for the independent effects of cognition on health outcomes, and there continues to be drive towards bringing together epidemiologists and differential psychologists (Deary, Weiss, & Batty, 2010). To overlook individual differences in psychological traits,

and treat these as proxies to educational and social inequalities, will only reduce the utility of disease prediction models.

Bringing cognitive epidemiology to cognitive ageing research

A final recommendation is a methodological one and relates to the field of cognitive ageing research, in respect of 1) reverse causation and 2) attrition bias.

This thesis found associations between cognition and disease biomarkers, detectable at preclinical stages of disease, and some contemporaneous associations in midlife that were partially or fully explained by cognition in youth. This highlights the need for researchers in ageing to consider the lifetime raft of exchanges between cognitive and biological factors, influenced by environmental stressors, and to take account of potential reverse causation when making inferences about disease impact on cognitive function.

Furthermore, the potential hazards of survival and attrition bias were brought to the fore in the latter chapters by unexpected positive associations between reaction times and disease biomarkers. It is possible therefore, that among older adult research cohorts exist a cluster of high ability individuals apparently resilient to disease and ageing processes, or managing to function relatively well in spite of them. The impact of this form of selection bias should not be underestimated and may be contributing to false positive results, or indeed null associations, in the cognitive ageing literature.

Final Summary

The main focus of this thesis was to investigate social and behavioural influences on pathways from intelligence differences to all-cause mortality and CVD-risk in the general population. Additional to this was an indirect testing of an alternative theory in cognitive epidemiology, that of underlying system integrity. It is clear that socioeconomic factors can be both confounders and mediators of the IQ-mortality link, and can cause statistical overadjustment in models, but this thesis also

validates evidence of independent effects of cognition on health outcomes in addition to such influences. Psychometric intelligence performance and cognitive reaction time can predict later CVD biomarker status in healthy populations. However, routes of causation can still only be inferred, and future research would benefit from looking at the early life origins of these associations in conjunction with genetic influence. After all it is of interest to understand all contributory factors to disease risk so that, ultimately, preventative policy and practice can benefit.

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Appendices

Appendix A: Studies excluded from meta-analysis, *N* = 64

Ref #	Reference	Reason for exclusion
1	Aapro, M.S. (2007). It is too early to know if intelligence determines cancer incidence and survival. *Annals of Oncology*, *18*, 4-5.	Outcome is morbidity or cause-specific mortality
2	Anstey, K.J., Mack, H.A., & von Sanden, C. (2006). The relationship between cognition and mortality in patients with stroke, coronary heart disease, or cancer. *European Psychologist*, *11*, 182-195.	No empirical data
3	Arora, G., Polavarapu, N., & McDonald, J.F. (2009). Did natural selection for increased cognitive ability in humans lead to an elevated risk of cancer? *Medical Hypotheses*, *73*, 453-456.	Outcome is morbidity or cause-specific mortality
4	Baltes, P.B., & Baltes, M.M. (1990). *Successful Aging: Perspectives from the Behavioral Sciences*. New York, NY US, Cambridge University Press.	No empirical data
5	Baltes, P.B., Schaie, K.W., & Nardi, A.H. (1971). Age and experimental mortality in a seven-year longitudinal study of cognitive behavior. *Developmental Psychology*, *5*, 18-26.	General intelligence measured in adulthood
6	Batty, G.D., & Deary, I.J. (2004). Early life intelligence and adult health: Associations, plausible mechanisms, and public health importance are emerging. *British Medical Journal*, *329*, 585-586.	No empirical data
7	Batty, G.D., & Deary, I.J. (2005). Education and mortality: A role for intelligence? *Journal of Epidemiology & Community Health, 59,* 809-810. Comments on an article by F. V. van Oort, F. J. Van Lenthe and J. P. Mackenbach (see record 2005-01769-002).	No empirical data
8	Batty, G.D., & Deary, I.J. (2005). Health communication, intelligence, and health differentials. *American Journal of Public Health, 95*, 1088; author reply 1089.	No empirical data
9	Batty, G.D., & Deary, I.J. (2005). Intelligence, education, and transportation injury mortality. *Injury Prevention*, *11*, 318.	Outcome is morbidity or cause-specific mortality (and, no novel empirical data)

Ref #	Reference	Reason for exclusion
10	Batty, G.D., & Deary, I.J. (2005). Education and mortality: The role of intelligence. *Lancet*, *365*, 1765-1766.	No empirical data
11	Batty, G.D., Gale, C.R., Tynelius, P, Deary, I.J., & Rasmussen, F. (2009). IQ in early adulthood, socioeconomic position, and unintentional injury mortality by middle age: A cohort study of more than 1 million Swedish men. *American Journal of Epidemiology, 169*, 606-615.	Outcome is morbidity or cause-specific mortality
12	Batty, G.D., Mortensen, E.L., 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 & Perinatal Epidemiology*, *19*, 452-459.	Outcome is morbidity or cause-specific mortality
13	Batty, G.D., Der, G., Macintyre, S, & Deary, I.J. (2006). Does IQ explain socioeconomic inequalities in health? Evidence from a population based cohort study in the west of Scotland. *British Medical Journal*, *332*, 580-584.	General intelligence measured in adulthood
14	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 & Community Health*, *61*, 241-7.	Outcomes are risk factors for mortality
15	Batty, G.D., Deary, I.J., Schoon, I, & Gale, C.R. (2007). Mental ability across childhood in relation to risk factors for premature mortality in adult life: the 1970 British Cohort Study. *Journal of Epidemiology & Community Health*, *61*, 997-1003.	Outcomes are risk factors for mortality
16	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.	No empirical data
17	Batty, G.D., Deary, I.J., Tengstrom, A., & Rasmussen, F. (2008). IQ in early adulthood and later risk of death by homicide: cohort study of 1 million men. *British Journal of Psychiatry, 193*, 461-465.	Outcome is morbidity or cause-specific mortality
18	Batty, G.D., Wennerstad, K.M., Smith, G.D., Gunnell, D., Deary, I.J., Tynelius, P., & Rasmussen, F. (2007). IQ in early adulthood and later cancer risk: Cohort study of one million Swedish men. *Annals of Oncology*, *18*, 21-28.	Outcome is morbidity or cause-specific mortality
19	Batty, G.D., Mortensen, L.H., Gale, C.R., Shipley, M.J., Roberts, B.A., & Deary, I.J. (2009). IQ in late adolescence/early adulthood, risk factors in middle age, and later cancer mortality in men: The Vietnam Experience Study. *Psychooncology*, *18*, 1122-1126.	Outcome is morbidity or cause-specific mortality
20	Batty, G.D., Shipley, M.J., Mortensen, L.H., Gale, C.R., & Deary, I.J. (2008). IQ in late adolescence/early adulthood, risk factors in middle-age and later coronary heart disease	Outcome is morbidity or cause-specific mortality

Ref #	Reference	Reason for exclusion
	mortality in men: the Vietnam Experience Study. *European Journal of Cardiovascular Prevention and Rehabilitation*, *15*, 359-361.	
21	Batty, G.D., Shipley, M.J., Dundas, R., Macintyre, S., Der, G., Mortensen, L.H., & Deary, I.J. (2009). Does IQ explain socio-economic differentials in total and cardiovascular disease mortality? Comparison with the explanatory power of traditional cardiovascular disease risk factors in the Vietnam Experience Study. *European Heart Journal*, *30*, 1903-1909.	IQ-mortality association unreported
22	Bittles, A.H., Petterson, B.A., Sullivan, S.G., Hussain, R., Glasson, E.J., & Montgomery, P.D. (2002). The influence of intellectual disability on life expectancy. *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences, 57A*, M470-M472.	Clinical or unrepresentative sample
23	Bosworth, H.B., & Schaie, K.W. (1999). Survival effects in cognitive function, cognitive style, and sociodemographic variables in the Seattle Longitudinal Study. *Experimental Aging Research*, *25*, 121-139.	General intelligence measured in adulthood
24	Corley, J., Crang, J.A., & Deary, I.J. (2009). Childhood IQ and in-service mortality in Scottish army personnel during World War II. *Intelligence*, *37*, 238-242.	Clinical or unrepresentative sample
25	Deary, I. (2008). Why do intelligent people live longer? *Nature*, *456*, 175-176.	No empirical data
26	Deary, I.J. (2005). Intelligence, health and death. *The Psychologist*, *18*, 610-613.	No empirical data
27	Deary, I.J., & Batty, G.D. (2006). Commentary: pre-morbid IQ and later health--the rapidly evolving field of cognitive epidemiology. *International Journal of Epidemiology*, *35,* 670-672.	No empirical data
28	Deary, I.J., & Der, G. (2005). Reaction time explains IQ's association with death. *Psychological Science, 16*, 64-69.	Cognitive indicator is not a measure of general intelligence
29	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.	No empirical data
30	Deary, I.J., Whalley, L.J., et al. (2009). Childhood IQ and specific causes of death and mortality-related physical factors. In I.J. Deary, L.J. Whalley, & J.M. Starr (Eds.) *A Lifetime of Intelligence: Follow-up Studies of the Scottish Mental Surveys of 1932 and 1947* (pp. 69-83). Washington DC, U.S.: American Psychological Association.	Outcome is morbidity or cause-specific mortality

Ref #	Reference	Reason for exclusion
31	Deary, I.J., Whiteman, M.C., Pattie, A., Starr, J.M., Hayward, C., Wright, A.F., … Whalley, L.J. (2004). Apolipoprotein e gene variability and cognitive functions at age 79: a follow-up of the Scottish mental survey of 1932. *Psychology and Aging*, *19*, 367-371.	Outcomes are risk factors for mortality
32	Eide, M.G., Skjaerven, R., Irgens, L.M., Bjerkedal, T., & Overn, N. (2006). Associations of birth defects with adult intellectual performance, disability and mortality: Population-based cohort study. *Pediatric Research*, *59*, 848-853.	IQ-mortality association unreported
33	Eitinger, L., & Str, A. (1981). New investigations on the mortality and morbidity of Norwegian ex-concentration camp prisoners*. Israel Journal of Psychiatry and Related Sciences, 18*, 173-195.	Clinical or unrepresentative sample
34	Gale, C.R., Batty, G.D., & Deary, I.J. (2008). Locus of control at age 10 years and health outcomes and behaviors at age 30 years: the 1970 British Cohort Study. *Psychosomatic Medicine*, *70*, 397-403.	Outcomes are risk factors for mortality
35	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.	Outcome is morbidity or cause-specific mortality
36	Gottfredson, L.S. (2004). Life, death, and intelligence. *Journal of Cognitive Education and Psychology*, *4*, 23-46.	No empirical data
37	Gottfredson, L. S., & Deary, I.J. (2004). Intelligence Predicts Health and Longevity, but Why? *Current Directions in Psychological Science*, *13*, 1-4.	No empirical data
38	Gunnell, D., Magnusson, P.K.E., & Rasmussen, F. (2005). Low intelligence test scores in 18 year old men and risk of suicide: cohort study. *British Medical Journal*, *330*, 167.	Outcome is morbidity or cause-specific mortality
39	Hart, C.L., & Deary, I.J., MacKinnon, P.L., Davey Smith, G., Whalley, L.J., Wilson, V., Hole, D.J., & Starr, J.M. (2003). The Scottish mental survey 1932 linked to the Midspan studies: a prospective investigation of childhood intelligence and future health. *Public Health, 117*, 187-195.	Outcomes are risk factors for mortality
40	Hart, C.L., Taylor, M.D., Davey Smith, G., 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 and Medicine*, *59*, 2131-2138.	Outcome is morbidity or cause-specific mortality

Ref #	Reference	Reason for exclusion
41	Hemmingsson, T., Essen, J.V., Melin, B., Allebeck, P., & Lundberg, I. (2007). The association between cognitive ability measured at ages 18-20 and coronary heart disease in middle age among men: A prospective study using the Swedish 1969 conscription cohort. *Social Science and Medicine*, *65*, 1410-1419.	Outcome is morbidity or cause-specific mortality
42	Isager, T., Mouridsen, S.E., & Rich, B. (1999). Mortality and causes of death in pervasive developmental disorders. *Autism, 3,* 7-16.	Clinical or unrepresentative sample
43	Isohanni, I., Järvelin, M.R., Nieminen, P., Jones, P., Rantakallio, P., Jokelainen, J., & Isohanni, M. (1998). School performance as a predictor of psychiatric hospitalization in adult life: A 28-year follow-up in the Northern Finland 1966 birth cohort. *Psychological Medicine*, *28*, 967-974.	Outcome is morbidity or cause-specific mortality
44	Lawlor, D.A., Batty, G.D., Clark, H., Macintyre, S., & Leon, D.A. (2008). Association of childhood intelligence with risk of coronary heart disease and stroke: findings from the Aberdeen Children of the 1950s cohort study. *European Journal of Epidemiology*, *23*, 695-706.	Outcome is morbidity or cause-specific mortality
45	Lawlor, D.A., Clark, H., & Leon, D.A. (2007). Associations between childhood intelligence and hospital admissions for unintentional injuries in adulthood: the Aberdeen Children of the 1950s cohort study. *American Journal of Public Health*, *97*, 291-297.	Outcome is morbidity or cause-specific mortality
46	Lester, D. (1993). Intelligence and suicide in France: an ecological study. *Psychological Reports, 73*, 1226.	Outcome is morbidity or cause-specific mortality
47	Lester, D. (1995). Intelligence and suicide in Ireland and the United Kingdom. *Psychological Reports*, *77*, 122.	Outcome is morbidity or cause-specific mortality
48	Marmot, M., & Kivimaki, M. (2009). Social inequalities in mortality: A problem of cognitive function? *European Heart Journal*, *30*, 1819-1820.	No empirical data
49	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 & Community Health*, *58*, 674-679.	Outcome is morbidity or cause-specific mortality
50	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.	Outcome is morbidity or cause-specific mortality
51	Osler, M., & Batty, G.D. (2004). Commentary: influence of early life intelligence test performance on later health: do lower scoring children become less healthy adults? *International Journal of Epidemiology*, *33*, 414-5.	No empirical data

Ref #	Reference	Reason for exclusion
52	Osler, M., Andersen, A.M., Laursen, B., & Lawlor, D.A. (2007). Cognitive function in childhood and early adulthood and injuries later in life: the Metropolit 1953 male birth cohort. *International Journal of Epidemiology*, *36*, 212-219.	Outcome is morbidity or cause-specific mortality
53	Osler, M., Gottfredsen, N.S., & Prescott, E. (2008). Childhood social circumstances and health behaviour in midlife: The Metropolit 1953 Danish male birth cohort. *International Journal of Epidemiology*, *37*, 1367-1374.	Outcomes are risk factors for mortality
54	O'Toole, B.I. (1990). Intelligence and behaviour and motor vehicle accident mortality. *Accident; Analysis and Prevention*, *22*, 211-221.	Outcome is morbidity or cause-specific mortality
55	Roberts, B.A., Der, G., Deary, I.J., & Batty, G.D. (2009). Reaction time and established risk factors for total and cardiovascular disease mortality: Comparison of effect estimates in the follow-up of a large, UK-wide, general-population based survey. *Intelligence*, *37*, 561-566.	Cognitive measure not indicator of general intelligence
56	Roberts, B.W., Kuncel, N.R., Shiner, R., Caspi, A., & Goldberg, L.R. (2007). The power of personality: The comparative validity of personality traits, socioeconomic status, and cognitive ability for predicting important life outcomes. *Perspectives on Psychological Science*, *2,* 313-345.	No empirical data
57	Shipley, B.A., Der, G., Taylor, M.D., & Deary, I.J. (2006). Cognition and all-cause mortality across the entire adult age range: Health and Lifestyle Survey. *Psychosomatic Medicine*, *68*, 17-24.	General intelligence measured in adulthood
58	Shipley, B.A., Der, G., Taylor, M.D., & Deary, I.J. (2007). Association between mortality and cognitive change over 7 years in a large representative sample of UK residents. *Psychosomatic Medicine*, 69, 640-650.	General intelligence measured in adulthood
59	Shipley, B.A., Der, G., Taylor, M.D., & Deary, I.J. (2008). Cognition and mortality from the major causes of death: The Health and Lifestyle Survey. *Journal of Psychosomatic Research*, *65*, 143-152.	General intelligence measured in adulthood
60	Silventoinen, K., Modig-Wennerstad, K., Tynelius, P., & Rasmussen, F. (2007). Association between intelligence and coronary heart disease mortality: A population-based cohort study of 682 361 Swedish men. *Euroepan Journal of Cardiovascular Prevention and Rehabilitation*, *14*, 555-560.	Outcome is morbidity or cause-specific mortality
61	Singh-Manoux, A., Ferrie, J.E., Lynch, J.W., & Marmot, M. (2005). The role of cognitive ability (intelligence) in explaining the association between socioeconomic position and health: evidence from the Whitehall II prospective cohort study. *American Journal of Epidemiology*, *161*,	Outcome is morbidity or cause-specific mortality

Ref #	Reference	Reason for exclusion
	831-839.	
62	Snowdon, D.A., Greiner, L.H., & Markesbery, W.R. (2000). Linguistic ability in early life and the neuropathology of Alzheimer's disease and cerebrovascular disease: Findings from the Nun Study. *Annals of the New York Academy of Sciences*, *903*, 34-38.	Outcomes are risk factors for mortality
63	Taylor, M.D., Hart, C.L., Smith, G.D., Starr, J.M., Hole, D.J., Whalley, L.J., Wilson, V., & Deary, I.J. (2005). Childhood IQ and social factors on smoking behaviour, lung function and smoking-related outcomes in adulthood: Linking the Scottish Mental Survey 1932 and the Midspan studies. *British Journal of Health Psychology*, *10*, 399-410.	Outcomes are risk factors for mortality
64	van Boxtel, M.P., Buntinx, F., Houx, P.J., Metsemakers, J.F., Knottnerus, A., & Jolles, J. (1998). The relation between morbidity and cognitive performance in a normal aging population. The *Journals of Gerontology, Series A Biological Sciences & Medical Sciences*, *53*, M147-54.	General intelligence measured in adulthood

Appendix B: Studies included in meta-analysis, *N* = 16

1. Batty, G.D., Shipley, M.J., Mortensen, L.H., Boyle, S.H., Barefoot, J., Gronbaek, M., … Deary, I.J. (2008). IQ in late adolescence/early adulthood, risk factors in middle age and later all-cause mortality in men: The Vietnam Experience Study. *Journal of Epidemiology and Community Health*, *62*, 522-531.
2. Batty, G.D., Wennerstad, K.M., Davey Smith, G., Gunnell, D., Deary, I.J., Tylenius, P., & Rasmussen, F. (2009). IQ in early adulthood and mortality by middle age: Cohort study of one million Swedish men. *Epidemiology*, *20*, 100-109.
3. Deary, I.J., Batty, G.D., Pattie, A., & Gale, C.R. (2008). More intelligent, more dependable children live longer: A 55-year longitudinal study of a representative sample of the Scottish nation. *Psychological Science*, *19*, 874–880.
4. Hart, C.L., Taylor, M.D., Davey Smith, G., Whalley, L.J., Starr, J.M., Hole, D.J., (…) Deary, I.J. (2003). Childhood IQ, social class, deprivation, and their relationships with mortality and morbidity risk in later life: Prospective observational study linking the Scottish Mental Survey 1932 and the Midspan studies. *Psychosomatic Medicine*, *65*, 877-883.
5. Hemmingsson, T., Melin, B., Allebeck, P., & Lundberg, I. (2006). The association between cognitive ability measured at ages 18-20 and mortality during 30 years of follow-up – a prospective observational study among Swedish males born 1949-51. *International Journal of Epidemiology*, *35*, 665-670.
6. Holsinger, T., Helms, M., & Plassman, B. (2007). Intelligence in early adulthood and life span up to 65 years later in male elderly twins. *Age and Ageing*, *36*, 286–291.
7. Jokela, M., Batty, G.D., Deary, I.J., Gale, C.R., & Kivimaki, M. (2009). Low Childhood IQ and Early Adult Mortality: The Role of explanatory factors in the 1958 British Birth Cohort. *Pediatrics, 124*, e380-8.
8. Jokela, M., Elovainio, M., Singh-Manoux, A., & Kivimaki, M. (2009). IQ, socioeconomic status, and early death: The US National Longitudinal Survey of Youth. *Psychomatic Medicine, 71*, 322-328.
9. Kuh, D., Shah, I., Richards, M., Mishra, G., Wadsworth, M., & Hardy, R. (2009). Do childhood cognitive ability or smoking behaviour explain the influence of lifetime socioeconomic conditions on premature adult mortality in a British post war birth cohort? *Social Science and Medicine, 68*, 1565-1573.
10. Lager, A., Bremberg, S., & Vagero, D. (2009). The association of early IQ and education with mortality: 65 year longitudinal study in Malmo, Sweden. *British Medical Journal, 339*, b5282.
11. Leon, D.A., Lawlor, D.A., Clark, H., Batty, G.D., & Macintyre, S. (2009). The association of childhood intelligence with mortality risk from adolescence to middle age: findings from the Aberdeen Children of the 1950s cohort study. *Intelligence*, *37*, 520-528.
12. Martin, L.T., & Kubzansky, L.D. (2005). Childhood cognitive performance and risk of mortality: A prospective cohort study of gifted individuals. *American Journal of Epidemiology, 162*, 887-890.
13. O'Toole, B.I., Adena, M.A., & Jones, M.P. (1988). Risk factors for mortality in Australian Vietnam-era national servicemen: A case-control study. *Community Health Studies*, *12*, 408-417.
14. Osler, M., Andersen, A.M., Due, P., Lund, R., Damsgaard, M.T., & Holstein, B.E. (2003). Socioeconomic position in early life, birth weight, childhood cognitive function, and adult mortality: A longitudinal study of Danish men born in 1953. *Journal of Epidemiology and Community Health, 57*, 681-686.
15. Pearce, M.S., Deary, I.J., Young, A.H., & Parker, L. (2006). Childhood IQ and deaths up to middle age: The Newcastle Thousand Families Study. *Public Health, 120*, 1020-1026.
16. Whalley LJ, & Deary IJ. (2001). Longitudinal cohort study of childhood IQ and survival up to age 76. *British Medical Journal, 322*, 819.

Appendix C. Associations between biomarkers in the 1958 NCDS

	CRP	Fibrinogen	D-dimer	t-PA antigen	vWF antigen
CRP		0.56	0.27	0.27	0.19
Fibrinogen	*7,632*		0.33	0.15	0.23
D-dimer	*7,560*	*7,528*		0.00	0.18
t-PA antigen	*7,630*	*7,591*	*7,523*		0.17
vWF antigen	*7,659*	*7,621*	*7,551*	*7,623*	

Note. Values are Pearson's product moment correlation coefficients; italicised values are sample sizes.

Appendix D. Univariate and Multivariate Parameter Estimate Formulae

(i) The proportions of variance attributed to additive genetic ($\hat{h}^2$), shared environment ($\hat{c}^2$) and unique environment ($\hat{e}^2$) effects in univariate models were estimated for intelligence and academic achievement scores, as:

$$\hat{h}^2 = 2(\hat{t}_{SS} - \hat{t}_{OS}) / \hat{p}$$
$$\hat{c}^2 = \left[\hat{t}_{OS}(1+\hat{p}) - \hat{t}_{SS}\right] / \hat{p}$$
$$\hat{e}^2 = 1 - \left(\hat{c}^2 + \hat{h}^2\right)$$

where $\hat{p}$ is the estimated proportion of MZ twins among same sex pairs (Benyamin et al. 2005), and $\hat{t}$ denotes the intra-class correlations from the between and within-pair variances for same-sex ($\hat{t}_{SS}$) and opposite-sex ($\hat{t}_{OS}$) twins respectively. Proportion of variance due to unique variance ($\hat{e}^2$) is estimated from deducting the previously estimated parameters ($\hat{h}^2 + \hat{c}^2$) from unity.

(ii) Additive genetic ($\hat{r}_G$) and shared ($\hat{r}_C$) environmental correlations were estimated using:

$$\hat{r}_G = 2\left(\hat{r}_{12(SS)} - \hat{r}_{12(OS)}\right) / \left(\hat{p}\hat{h}_1\hat{h}_2\right)$$
$$\hat{r}_C = \left[(\hat{p}+1)\hat{r}_{12(OS)} - \hat{r}_{12(SS)}\right] / \left(\hat{p}\hat{c}_1\hat{c}_2\right)$$

where $\hat{r}$ is the correlation coefficient between two traits for SS ($\hat{r}_{12(SS)}$) and OS ($\hat{r}_{12(OS)}$) twin pairs respectively, and where $\hat{h}_1$ and $\hat{h}_2$ represent the square roots of the univariate heritability estimates for traits 1 and 2 respectively, and $\hat{c}_1$ and $\hat{c}_2$ represent the square roots of the shared environment parameters for traits 1 and 2.

(iii) In models to estimate bivariate heritability (Biv $\hat{h}^2$)—that is, the proportion of phenotypic covariance due to additive genetic factors (i.e. the ratio of additive genetic to phenotypic covariance)—and proportions of covariance due to shared (Biv $\hat{c}^2$) and unique environmental influence (Biv $\hat{e}^2$), the following formulae were used:

$$Biv\hat{h}^2 = \left[\sqrt{(\hat{h}^2{}_1)}\sqrt{(\hat{h}^2{}_2)}\hat{r}_G\right] / \hat{r}_p$$

$$Biv\hat{c}^2 = \left[\sqrt{(\hat{c}^2{}_1)}\sqrt{(\hat{c}^2{}_2)}\hat{r}_C\right] / \hat{r}_p$$

$$Biv\hat{e}^2 = 1 - \left[Biv\hat{c}^2 + Biv\hat{h}^2\right]$$

where $\hat{r}_p$ is the phenotypic correlation between two traits, $\hat{h}^2{}_1$ is the heritability estimate for trait 1, $\hat{h}^2{}_2$ is the heritability estimate for trait 2, and so on.

Appendix E. Correlations among the Twenty-07 study variables

1972 cohort

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.
1. Simple *m* wave1	1	**.61**	**.50**	**.26**	**-.11**	**-.18**	**-.13**	.07	.06	-.02	**.33**	**.15**	**.30**	**.21**	.07	.07	.05
2. Simple *sd* wave1		1	**.27**	**.21**	-.06	**-.11**	**-.08**	.02	.02	.04	**.16**	**.10**	**.15**	**.11**	.06	.04	**.08**
3. Choice *m* wave1			1	**.66**	**-.15**	**-.21**	**-.23**	.06	.07	-.02	**.28**	**.22**	**.53**	**.35**	.07	**.07**	**.11**
4. Choice *sd* wave1				1	**-.13**	**-.17**	**-.22**	.06	.05	-.03	**.18**	**.20**	**.38**	**.33**	.05	.07	**.09**
5. SES wave1					1	**.29**	**.38**	-.07	**-.13**	-.00	**-.09**	**-.08**	**-.19**	**-.10**	**-.15**	**-.11**	**-.14**
6. SES wave5						1	**.42**	-.04	**-.09**	-.04	**-.13**	**-.08**	**-.19**	**-.11**	-.05	-.07	**-.09**
7. Education							1	-.03	**-.11**	-.03	**-.13**	**-.13**	**-.23**	**-.15**	**-.14**	**-.12**	**-.13**
8. Heart rate wave1								1	**.29**	**-.13**	.02	.07	**.08**	.05	.00	.06	**-.10**
9. Heart rate wave5									1	-.04	.03	.06	**.08**	.06	**.18**	**.16**	**.18**
10. WHR wave1										1	.04	-.05	-.01	**-.16**	**-.09**	**-.10**	**.28**
11. Simple *m* wave5											1	**.57**	**.53**	**.26**	.04	.01	.01
12. Simple *sd* wave5												1	**.32**	**.24**	**.08**	.01	-.02
13. Choice *m* wave5													1	**.59**	.06	.06	**.10**
14. Choice *sd* wave5														1	.06	**.09**	-.01
15. CRP															1	**.57**	**.32**
16. Fibrinogen																1	**.19**
17. Meta component																	1

Note. Sample sizes for correlation coefficients are in the range, n = 711 to 758. Coefficients in bold are statistically significant, $p < .05$

1952 cohort

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.
1. Simple *m* wave1	1	**.59**	**.20**	**.51**	**-.23**	**-.21**	**-.21**	.03	.04	-.05	**.39**	**.18**	**.33**	**.20**	.04	.04	.02
2. Simple *sd* wave1		1	**.21**	**.31**	**-.11**	**-.12**	**-.07**	.06	.04	-.03	**.26**	**.25**	**.22**	**.17**	.03	.02	.02
3. Choice *m* wave1			1	**.51**	**-.17**	**-.19**	**-.15**	**.10**	**.08**	**-.12**	**.17**	**.17**	**.37**	**.40**	.02	.04	-.01
4. Choice *sd* wave1				1	**-.32**	**-.29**	**-.25**	.06	**.09**	.02	**.35**	**.24**	**.60**	**.39**	.05	.06	.05
5. SES wave1					1	**.63**	**.57**	-.05	**-.14**	.00	**-.20**	**-.12**	**-.29**	**-.21**	**-.09**	**-.08**	**-.10**
6. SES wave5						1	**.50**	**-.16**	**-.18**	.01	**-.15**	**-.17**	**-.29**	**-.25**	**-.15**	**-.11**	**-.09**
7. Education							1	**-.07**	**-.11**	-.01	**-.18**	**-.11**	**-.23**	**-.21**	**-.09**	-.03	**-.13**
8. Heart rate wave1								1	**.30**	**-.12**	.02	.04	-.00	**.08**	**.13**	**.14**	**.11**
9. Heart rate wave5									1	.01	**.12**	**.08**	**.15**	**.14**	**.17**	**.21**	**.19**
10. WHR wave1										1	-.00	-.01	.05	**-.08**	-.05	-.04	**.34**
11. Simple *m* wave5											1	**.66**	**.52**	**.27**	**.08**	.05	.07
12. Simple *sd* wave5												1	**.33**	**.24**	.03	.02	.02
13. Choice *m* wave5													1	**.54**	**.13**	**.07**	**.12**
14. Choice *sd* wave5														1	**.16**	**.10**	.04
15. CRP															1	**.47**	**.33**
16. Fibrinogen																1	**.11**
17. Meta component																	1

Note. Sample sizes for correlation coefficients are in the range, n = 781 to 836. Coefficients in bold are statistically significant, $p < .05$

1932 cohort

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.
1. Simple *m* wave1	1	**.63**	**.45**	**.09**	**-.16**	**-.14**	**-.22**	.04	.00	**.09**	**.27**	**.13**	**.23**	.05	.02	-.04	.04
2. Simple *sd* wave1		1	**.22**	**.16**	**-.10**	**-.11**	**-.12**	.04	-.01	.01	**.19**	**.14**	**.15**	**.09**	.00	.04	-.01
3. Choice *m* wave1			1	**.31**	**-.24**	**-.24**	**-.28**	-.00	.02	.08	**.21**	**.15**	**.38**	**.15**	.02	-.07	.00
4. Choice *sd* wave1				1	**-.09**	**-.11**	**-.12**	-.02	.01	**-.16**	.08	.08	**.23**	**.24**	-.04	-.04	-.05
5. SES wave1					1	**.77**	**.47**	.03	**-.09**	-.01	**-.20**	**-.16**	**-.24**	**-.09**	-.08	-.04	.03
6. SES wave5						1	**.49**	-.02	**-.14**	-.01	**-.15**	**-.10**	**-.26**	**-.12**	-.06	.00	.05
7. Education							1	.04	-.09	-.04	**-.20**	**-.14**	**-.20**	**-.09**	-.08	-.03	-.03
8. Heart rate wave1								1	**.22**	.03	.06	.03	.10	.08	.07	**.12**	-.01
9. Heart rate wave5									1	**-.10**	.06	.05	**.10**	.08	**.19**	**.18**	.01
10. WHR wave1										1	.04	.05	.04	-.04	.03	-.02	**.27**
11. Simple *m* wave5											1	**.74**	**.60**	**.28**	.07	-.01	-.01
12. Simple *sd* wave5												1	**.39**	**.20**	.03	-.02	-.03
13. Choice *m* wave5													1	**.66**	**.11**	-.01	-.01
14. Choice *sd* wave5														1	**.14**	.02	-.03
15. CRP															1	**.50**	**.14**
16. Fibrinogen																1	**.10**
17. Meta component																	1

Note. Sample sizes for correlation coefficients are in the range, n = 353 to 528. Coefficients in bold are statistically significant, $p < .05$

Appendix F. Categorical group differences in the Twenty-07 study

1972 cohort

	Smoker w1			Smoker w5		
	Yes	No	test	Yes	No	test
SimpleRT *m* wave1	0.27 (1.35) *n* = 117	-0.06 (0.86) *n* = 621	*Z* = -2.53 *p* = .02	0.12 (1.09) *n* = 198	-0.06 (0.90) *n* = 538	*Z* = -2.39 *p* = .02
SimpleRT *sd* wave1	0.15 (1.34) *n* = 117	-0.04 (0.89) *n* = 619	*Z* = -0.74 *p* = .46	0.05 (1.04) *n* = 197	-0.03 (0.95) *n* = 537	*Z* = -1.27 *p* = .20
ChoiceRT *m* wave1	0.23 (1.24) *n* = 117	-0.06 (0.93) *n* = 618	*Z* = -1.96 *p* = .05	0.29 (1.08) *n* = 197	-0.12 (0.94) *n* = 536	*Z* = -4.80 *p* < .001
ChoiceRT *sd* wave1	0.27 (1.20) *n* = 117	-0.04 (0.98) *n* = 619	*Z* = -2.80 *p* = .005	0.24 (1.01) *n* = 197	-0.07 (1.02) *n* = 537	*Z* = -4.43 *p* < .001
SES wave1	3.59 (1.39) *n* = 122	4.06 (1.23) *n* = 628	*t* (748) = 3.82 *p* < .001	3.69 (1.26) *n* = 201	4.09 (1.25) *n* = 547	*t* (746) = 3.87 *p* < .001
SES wave5	4.18 (1.12) *n* = 124	4.62 (1.04) *n* = 634	*t* (756) = 4.23 *p* < .001	4.04 (1.19) *n* = 205	4.73 (0.96) *n* = 551	*t* (754) = 8.18 *p* < .001
Education	12.6 (2.67) *n* = 125	14.2 (3.17) *n* = 632	*t* (755) = 5.31 *p* < .001	12.9 (2.76) *n* = 205	14.3 (3.20) *n* = 552	*t* (755) = 5.62 *p* < .001
Heart rate wave1	75.5 (10.5) N = 117	72.4 (9.79) N = 623	*t* (738) = -3.07 *p* = .002	73.0 (9.62) N = 197	72.9 (10.1) N = 541	*t* (736) = -.078 *p* = .94
Heart rate wave5	68.2 (10.4) N = 125	65.4 (10.2) N = 630	*t* (753) = -2.84 *p* = .005	67.8 (10.2) N = 205	65.1 (10.2 N = 549	*t* (752) = -3.26 *p* < .001
WHR wave1	.850 (.067) N = 117	.855 (.071) N = 624	*t* (739) = .62 *p* = .53	.863 (.076) N = 199	.850 (.068) N = 540	*t* (737) = -2.19 *p* = .03
CRP	0.30 (0.51) *n* = 122	0.20 (0.48) *n* = 629	*t* (749) = -2.23 *p* = .03	0.26 (0.48) *n* = 203	0.19 (0.48) *n* = 546	*t* (751) = -2.27 *p* = .02
Fibrinogen	3.42 (0.75) *n* = 122	3.28 (0.65) *n* = 620	*t* (740) = -2.00 *p* = .05	3.45 (0.71) *n* = 201	3.25 (0.65) *n* = 539	*t* (738) = -3.69 *p* < .001
Metabolic comp.	.17 (1.10) *n* = 119	-.03 (0.98) *n* = 614	*t* (731) = -2.00 *p* = .05	.25 (1.02) *n* = 199	-.09 (0.98) *n* = 533	*t* (730) = -4.20 *p* < .001
MetS	Yes: 18.2% No: 15.9%	Yes: 81.8% No: 84.1%	χ2 (1) = .48 *p* = .49	Yes: 29.2% No: 26.6%	Yes: 70.8% No: 73.4%	χ2 (1) = .41 *p* = .52

1952 cohort

	Wave1			Wave5		
	Smoker	Non-smoker	test	Smoker	Non-smoker	test
SimpleRT *m* wave1	0.01 (1.07) *n* = 345	-0.01 (0.95) *n* = 470	*Z* = -.103 *p* = .92	0.09 (1.02) *n* = 212	-0.03 (0.99) *n* = 606	*Z* = -1.79 *p* = .07
SimpleRT *sd* wave1	0.06 (1.14) *n* = 345	-0.04 (0.89) *n* = 470	*Z* = -.498 *p* = .62	0.10 (1.06) *n* = 212	-0.04 (0.98) *n* = 606	*Z* = -1.54 *p* = .13
ChoiceRT *m* wave1	0.10 (1.05) *n* = 340	-0.08 (0.95) *n* = 468	*Z* = -2.64 *p* = .008	0.18 (1.06) *n* = 209	-0.06 (0.97) *n* = 602	*Z* = -3.32 *p* = .001
ChoiceRT *sd* wave1	0.10 (1.09) *n* = 340	-0.07 (0.92) *n* = 467	*Z* = -1.77 *p* = .08	0.11 (1.01) *n* = 209	-0.04 (0.99) *n* = 601	*Z* = -2.36 *p* < .02
SES wave1	3.80 (1.30) *n* = 352	4.40 (1.22) *n* = 484	*t* (834) = 6.77 *p* < .001	3.55 (1.29) *N* = 212	4.35 (1.22) *n* = 624	*t* (834) = 8.13 *p* < .001
SES wave5	3.99 (1.37) *n* = 354	4.52 (1.16) *n* = 485	*t* (837) = 6.13 *p* < .001	3.70 (1.40) *n* = 15	4.49 (1.17) *n* = 627	*t* (840) = 8.11 *p* < .001
Education	12.1 (2.92) *n* = 350	13.1 (3.25) *n* = 483	*t* (831) = 4.86 *p* < .001	11.6 (2.51) *n* = 212	13.1 (3.29) *n* = 625	*t* (835) = 5.90 *p* < .001
Heart rate wave1	71.9 (9.68) *n* = 338	70.1 (9.75) *n* = 469	*t* (805) = -2.57 *p* = .010	73.2 (9.47) *n* = 208	70.0 (9.73) *n* = 602	*t* (808) = -4.13 *p* < .001
Heart rate wave5	67.2 (11.5) *n* = 344	65.8 (10.3) *n* = 478	*t* (820) = -1.79 *p* = .07	69.3 (11.3) *n* = 209	65.4 (10.5) *n* = 617	*t* (824) = -4.59 *p* < .001
WHR wave1	.881 (.087) *n* = 335	.875 (.090) *n* = 465	*t* (798) = -0.91 *p* = .37	.873 (.089) *n* = 205	.880 (.088) *n* = 598	*t* (801) = 1.04 *p* = .30
CRP	0.44 (0.45) *n* = 349	0.26 (0.46) *n* = 481	*t* (828) = -5.73 *p* < .001	0.46 (0.43) *n* = 213	0.30 (0.47) *n* = 620	*t* (829) = -0.82 *p* < .001
Fibrinogen	3.68 (0.70) *n* = 345	3.47 (0.68) *n* = 470	*t* (813) = -4.33 *p* < .001	3.77 (0.75) *n* = 213	3.48 (0.66) *n* = 605	*t* (816) = -5.35 *p* < .001
Metabolic comp.	.16 (1.04) *n* = 347	-.13 (0.96) *n* = 469	*t* (814) = -4.12 *p* < .001	.14 (1.08) *n* = 212	-.05 (0.97) *n* = 608	*t* (818) = -2.29 *p* = .02
MetS	Yes: 45.2% No: 40.8%	Yes: 54.8% No: 59.2%	χ2 (1) = 1.55 *p* = .21	Yes: 26.9% No: 25.3%	Yes: 73.1% No: 74.7%	χ2 (1) = .27 *p* = .60

1932 cohort

	Wave1			Wave5		
	Smoker	Non-smoker	test	Smoker	Non-smoker	test
SimpleRT *m* wave1	0.07 (1.03) *n* = 178	-0.03 (0.98) *n* = 341	*Z* = 1.30 *p* = .20	0.10 (1.02) *n* = 83	-0.03 (0.99) *n* = 434	*Z* = -1.06 *p* = .29
SimpleRT *sd* wave1	-0.04 (0.87) *n* = 178	0.02 (1.06) *n* = 341	*Z* = -0.24 *p* = .81	0.03 (0.89) *n* = 83	-0.01 (1.02) *n* = 434	*Z* = -.810 *p* = .42
ChoiceRT *m* wave1	0.25 (0.95) *n* = 176	-0.13 (1.00) *n* = 341	*Z* = -3.85 *p* < .001	0.24 (1.01) *n* = 82	-0.06 (0.98) *n* = 433	*Z* = -2.29 *p* = .02
ChoiceRT *sd* wave1	0.14 (1.14) *n* = 176	-0.07 (0.91) *n* = 341	*Z* = -1.76 *p* = .08	0.28 (1.25) *n* = 82	-0.06 (0.93) *n* = 433	*Z* = -2.36 *p* = .02
SES wave1	3.66 (1.39) *n* = 180	4.05 (1.27) *n* = 348	*t* (526) = 3.27 *p* = .001	3.45 (1.43) *n* = 84	4.00 (1.29) *n* = 442	*t* (524) = 3.53 *p* < .001
SES wave5	3.39 (1.41) *n* = 180	3.93 (1.34) *n* = 348	*t* (526) = 4.30 *p* < .001	3.23 (1.48) *n* = 84	3.84 (1.35) *n* = 442	*t* (524) = 3.77 *p* < .001
Education	9.99 (2.20) *n* = 171	10.9 (3.06) *n* = 335	*t* (504) = 3.61 *p* < .001	9.95 (2.35) *n* = 79	10.8 (2.89) *n* = 426	*t* (503) = 2.33 *p* = .02
Heart rate wave1	73.6 (8.56) *n* = 120	70.0 (9.13) *n* = 235	*t* (353) = -3.65 *p* < .001	74.1 (8.32) *n* = 56	70.7 (9.15) *n* = 298	*t* (352) = -2.63 *p* = .009
Heart rate wave5	67.4 (11.3) *n* = 173	64.6 (10.8) *n* = 335	*t* (506) = -2.72 *p* = .007	67.0 (12.1) *n* = 81	65.3 (10.8) *n* = 425	*t* (504) = -1.31 *p* = .19
WHR wave1	.871 (.077) *n* = 179	.854 (.080) *n* = 343	*t* (520) = -2.26 *p* < .001	.873 (.074) *n* = 84	.857 (.080) *n* = 436	*t* (518) = -1.71 *p* = .09
CRP	0.53 (0.43) *n* = 177	0.43 (0.41) *n* = 346	*t* (521) = -2.58 *p* = .01	0.51 (0.40) *n* = 83	0.45 (0.42) *n* = 438	*t* (519) = -1.13 *p* = .26
Fibrinogen	3.80 (0.79) *n* = 170	3.71 (0.72) *n* = 335	*t* (503) = -1.19 *p* = .24	3.88 (0.85) *n* = 80	3.72 (0.72) *n* = 423	*t* (501) = -1.77 *p* = .08
Metabolic comp	.02 (1.04) *n* = 172	-.01 (0.98) *n* = 338	*t* (508) = -.321 *p* = .75	.03 (1.02) *n* = 80	-.01 (1.00) *n* = 429	*t* (507) = -.280 *p* = .78
MetS	Yes: 33.5% No: 34.5%	Yes: 66.5% No: 65.5%	χ2 (1) = .05 *p* = .82	Yes: 13.3% No: 17.4%	Yes: 86.7% No: 82.6%	χ2 (1) = 1.51 *p* = .22

Appendix G. Inverse probability weights for wave5 of Twenty-07 Study

The following procedures were conducted by Shaun Seaman from the MRC Biostatistics Unit in Cambridge UK, and documented by him on 22/07/2010.

Introduction

In the Twenty-07 study not all subjects attended wave5, causing a problem for any analysis involving variables measured at wave5. One way to deal with this problem would be to restrict the analysis just to those subjects attending Wave5. However, these individuals may be unrepresentative of the full cohort, leading to biased estimation. Inverse probability weighting can be used to weight the set of the subjects attending Wave5 to make them more representative of the full cohort and hence reduce this bias.

This text explains how inverse-probability weights for wave5 of the Twenty-07 study were derived. Four sets of weights were derived: one for all subjects attending wave5; one for subjects attending all of waves 1–5; one for subjects providing a blood sample at wave5; and one for subjects attending all of waves 1–5 and providing a blood sample. The first set can be used if the analysis involves only variables measured at waves 1 and 5; the second, if it involves also variables measured at waves 2, 3 or 4. The third and fourth sets can be used if the analysis involves data from the blood samples.

Description of Wave-Missingness Pattern

4,510 subjects attended wave1. Of these, 3,861 (86%) were still alive at wave5. We assume that the purpose of any analysis is to make inference about the population still alive at the time of wave5. So, we weight the subjects who attended wave5 to make them representative of the whole set of 3,861 subjects still alive at wave5. 2,604 (67%) of the 3,861 subjects alive at the time of wave5 attended wave5; of these, 2242 (86%) gave a blood sample at wave5.

Non-monotone wave5 weights

We divided the subjects into eight sets according to the last wave they attend prior to wave5 and according to whether or not they are in the youngest cohort. We call this last attended wave prior to wave5 the ‘latest wave’. Due to the small number of subjects attending wave5 but not attending either wave3 or wave4, we combined the sets of subjects whose latest wave was 1 with those whose latest wave was 2. Thus, the eight sets were reduced to six.

For each of these six sets, a logistic regression model was specified for the probability that a subject in that set would attend wave5 and this model was fitted to

the subjects in that set. This model used as covariates the most up-to-date information available on a number of factors that may affect this probability. Thus, for example, in the set of subjects whose latest wave was 3, the covariates used included car ownership, drinking behaviour, etc. at wave3, whereas for those whose latest wave was 4, they included car ownership, drinking behaviour, etc. at wave4. For the set of subjects whose latest wave was 1 or 2, information at wave1 was used, as this was available for all subjects in the set. The regression model for the youngest cohort included more covariates than were in the model for the middle and oldest cohort, because the youngest cohort was asked additional questions, e.g. about school and involvement with the police. The 'non-monotone wave5 weights' are the inverse of the fitted probabilities from these logistic regression models.

The covariates used were:

- Whether in the Region or the Locality sample
- For subjects in the Locality sample, whether in South-West or North-West
- Sex
- Religion
- Car ownership
- Self-assessed health (4-level ordinal variable)
- Smoking (non, current, or ex)
- Alcohol Drinker (non, current, or ex)
- Whether returned self-completion questionnaire
- Social class (professional, other non-manual, or manual)
- Housing tenure
- Longstanding illness
- Housing (detached, semi-detached or terraced, flat or other)
- Marital status (never married, married, separated or divorced or widowed)
- Economic status (full-time education, employed, unemployed or government training scheme, caring or retired or disabled/sick)
- In hospital in previous year
- Log of total number of times in hospital ever at Wave1
- Carer
- Registered disabled
- Total IQ score from AH4

For the youngest cohort, the following variables were used in addition:

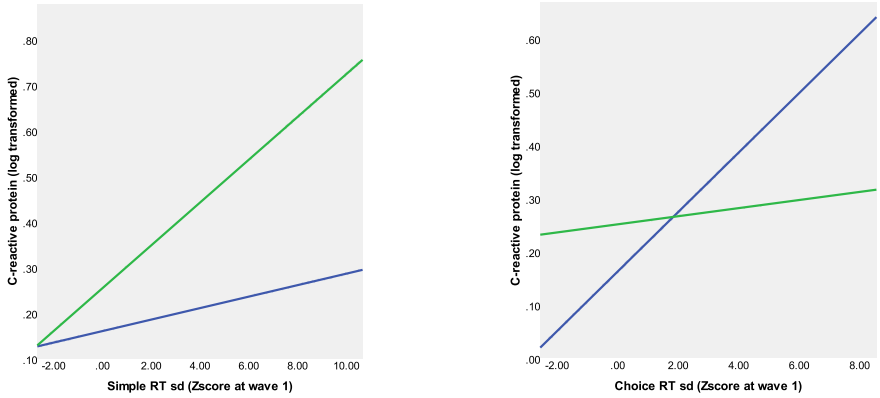
- Ever used drugs
- I cannot wait to leave school (measured at wave1 only)
- If I get a chance to dodge school I do (measured at wave1 only)
- Trouble with police or in court during 12 months prior to wave1
- Trouble with police since last interview

Weights for the wave5 Blood Sample

Corresponding to the non-monotone wave5 weight is the weight for the wave5 blood sample. The 'non-monotone blood weights' is suitable for an analysis involving only variables measured at waves 1 and 5 and in the blood sample. The probability that a subject attends wave5 and provides a blood sample is the product of the probability that he/she attends wave5 and the conditional probability that he/she provides a blood sample given that he/she has attended wave5. The estimation of the first of these probabilities was described above. The second probability was estimated using a logistic regression model, fitting it to the subjects attending wave5. The same set of factors as described above was used as covariates in this model, as usual using the latest recorded values of these factors, i.e. the values measured at wave5. The non-monotone blood weights are then the product of the two fitted probabilities.

Appendix G. Sex x RT interaction effects in predicting inflammatory status: Twenty-07 study

Sex x RT in predicting inflammatory biomarkers: 1972 cohort



Sex interacted with simple and choiceRT *sd* at wave1, in linear regression models predicting CRP:

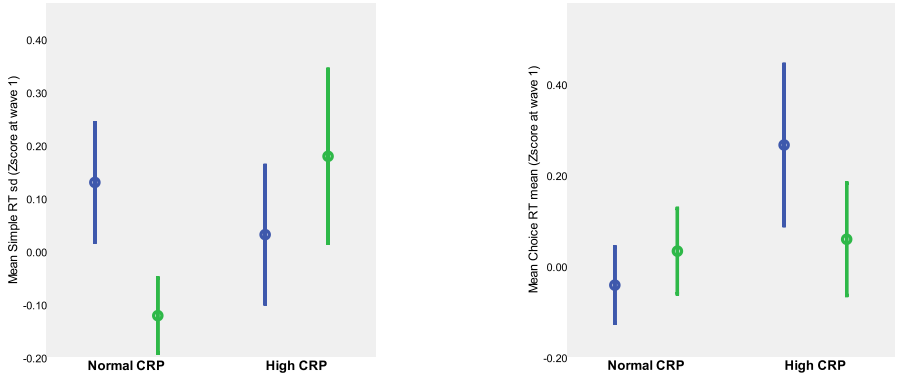
The association between baseline simpleRT *sd* and lower CRP levels 20 years later was only evident in females (green line) – see left chart above. In a linear regression model adjusting for age, oral contraceptives, sex, and simpleRT *sd,* the Sex x RT interaction effect was statistically significant:

Coefficient = .079 [95% CI .015 to .142], $p = .016$

The association between more consistent baseline choiceRT and lower CRP levels 20 years later was only evident in males (blue line) – see right chart above. In a linear regression model adjusting for age, oral contraceptives, sex, and choiceRT *sd,* the interaction effect was statistically significant:

Coefficient = -.075 [95% CI -.140 to -.011], $p = .022$

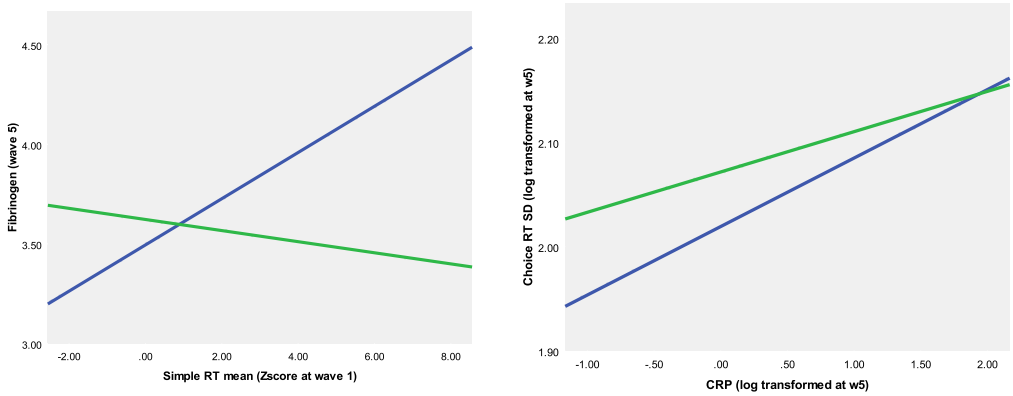
Sex x RT in predicting high CRP status: 1972 cohort



Sex x RT interaction effects reached statistical significance in logistic regression models predicting high CRP levels at wave5. The 95% CIs show these effects in men (blue) and women (green), which were significant for:

Sex x SimpleRT sd	*OR* = 0.69 [95% CI 0.55, 0.87], $p < .001$ (see left chart)
Sex x ChoiceRT m	*OR* = 1.28 [95% CI 1.02, 1.61], $p = .031$ (see right chart)
Sex x ChoiceRT sd	*OR* = 1.30 [95% CI 1.05, 1.61], $p = .015$

Sex x RT in predicting inflammatory biomarkers: 1952 cohort



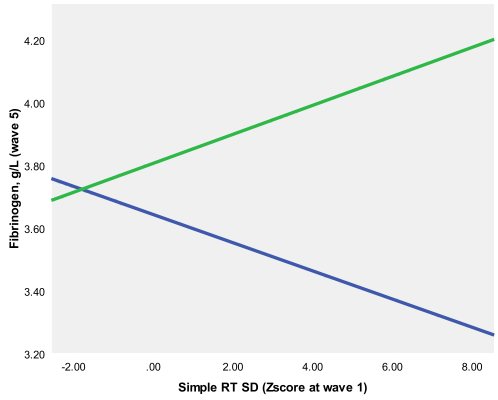
Sex interacted with simpleRT *m* at wave1 in predicting Fibrinogen. The association between faster simpleRT and lower fibrinogen 20 years later was only evident in men (blue line) – see chart above left. In a linear regression model adjusting for age, sex, and simpleRT mean, the Sex x RT interaction effect was statistically significant:

Coefficient = -.002 [95% CI -.003 to -.001], p = .006

At wave5 sex interacted with CRP in predicting ChoiceRT sd. The association between more consistent ChoiceRT and lower CRP was more evident in men (blue line) than women (green line) – see chart above right. The direction of association however was the same in both sex groups:

Coefficient = -.055 [95% CI -.099, -.011], p = .014

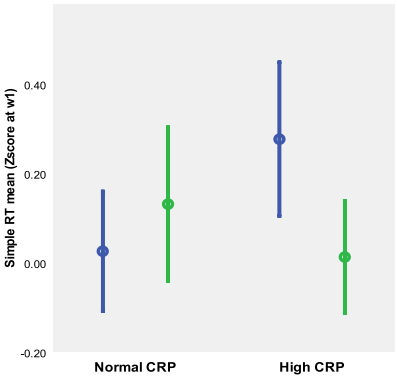
Sex x RT in predicting inflammatory biomarkers: 1932 cohort

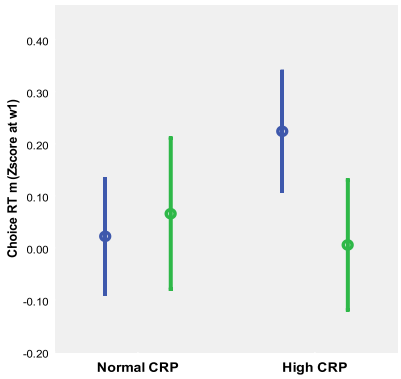


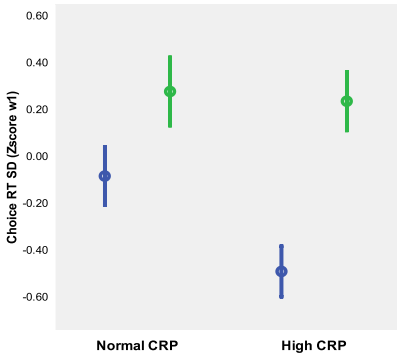
Sex interacted with simpleRT *sd* at wave1 in predicting Fibrinogen. The association between more consistent simpleRT and lower fibrinogen 20 years later was only evident in women (green line), and the reverse trend was seen for men. In a linear regression model adjusting for age, sex, and simpleRT mean, the Sex x RT interaction effect was statistically significant:

Coefficient = .728 [95% CI 0.165 to 1.290], $p = .011$

Sex x RT in predicting high CRP: 1952 cohort



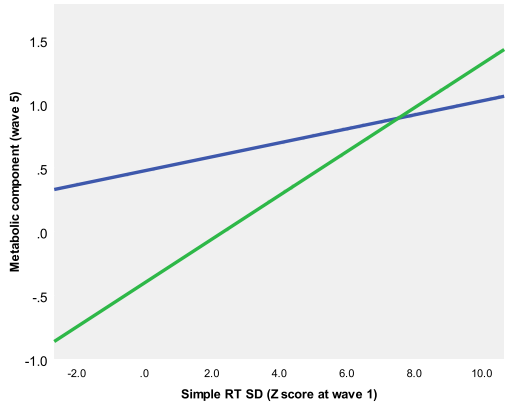




Sex x RT interaction effects reached statistical significance in logistic models predicting high CRP levels at wave5. These 95% CIs show the effects for men (blue) and women (green), which were significant for:

Sex x SimpleRT m	$OR = 2.31$, $SE = 1.10$, $p = .036$
Sex x ChoiceRT m	$OR = 5.94$, $SE = 2.35$, $p = .011$
Sex x ChoiceRT sd	$OR = -4.92$, $SE = 1.40$, $p < .001$

Appendix H. Sex x RT in predicting the metabolic component



Sex x RT interaction effects reached statistical significance in linear regression models predicting metabolic component score at wave5. The 95% CIs show these effects in men (blue) and women (green), which were significant for:

Sex x SimpleRT sd coefficient = .205 [.076, 0.334], p = .002