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Shared genetic aetiology between cognitive ability and cardiovascular disease risk factors: Generation Scotland's Scottish family health study

Michelle Luciano [a], G. David Batty [a,b,c], Mark McGilchrist [d], Pamela Linksted [e], Bridie Fitzpatrick [f], Cathy Jackson [g], Alison Pattie [a], Anna F. Dominiczak [h], Andrew D. Morris [i], Blair H. Smith [j], David Porteous [e], Ian J. Deary [a,*]

[a] Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK
[b] MRC Social and Public Health Sciences Unit, Glasgow, UK
[c] The George Institute for International Health, University of Sydney, Sydney, Australia
[d] University of Dundee, Health Informatics Centre, MacKenzie Building, Kirsty Semple Way, Dundee, UK
[e] Generation Scotland, the University of Edinburgh Molecular Medicine Centre, Western General Hospital, Edinburgh, UK
[f] University of Glasgow, Division of Community-Based Sciences, Glasgow, UK
[g] University of Dundee, Tayside Centre for General Practice, Kirsty Semple Way, Dundee, UK
[h] University of Glasgow, BHF Glasgow Cardiovascular Research Centre, 126 University Place, Glasgow, UK
[i] University of Dundee, Division of Medicine and Therapeutics, Level 7, Ninewells Hospital and Medical School, Dundee, UK
[j] University of Aberdeen, Department of General Practice and Primary Care, Foresterhill Health Centre, Westburn Road, Aberdeen, UK

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ABSTRACT

People with higher general cognitive ability in early life have more favourable levels of cardiovascular disease (CVD) risk factors in adulthood and CVD itself. The mechanism of these associations is not known. Here we examine whether general cognitive ability and CVD risk factors share genetic and/or environmental aetiology. In this large, pedigree-based cross-sectional study of Scottish families ($N = 1983$ families; 6086 individuals) we estimate the heritability (ranging from 0.08 to 0.91) of a diverse battery of CVD risk factors, and also examine the extent and causes of their relationship with general cognitive ability. General cognitive ability was associated significantly with almost all the risk factors investigated, explaining between 0.2% and 11% of variance. For those measures with an effect size greater than around 1%, the relationship was primarily influenced by genes (30 to 94%) rather than the environment. These findings have relevance to the growing field of cognitive epidemiology, in which intelligence is used to predict morbidity and mortality. We provide evidence that risk factors such as education and income – which are typically treated as environmental indicators by epidemiologists and controlled for in their studies of morbidity – are genetically confounded with IQ.

1. Introduction

Lower cognitive ability from early life, as measured by standard IQ tests, is associated with a greater risk of cardiovascular disease (CVD) (Batty et al., 2009; Deary & Batty, 2007; Hemmingsson, Melin, Allebeck, & Lundberg, 2006) and with less favourable levels of a range of well-established CVD risk factors such as obesity (Chandola, Deary, Blane, & Batty, 2006), cigarette smoking (Batty, Deary, & Macintyre, 2007) and the metabolic syndrome (Batty, Gale, Mortensen, Langenberg, Shipley, & Deary, 2008). The causes of these associations are unknown. The risk factors might be outcomes of cognitive ability, and then act as mediators between cognition and CVD: for example, those high in cognitive ability might choose healthier diets, which are then

* Corresponding author. Tel.: +44 131 650 3452; fax: +44 131 651 1771.
E-mail address: I.Deary@ed.ac.uk (I.J. Deary).

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protective against CVD. Alternatively, cognition and CVD risk factors might share antecedent causes, for example both might be influenced by environmental factors like healthcare, or reliant on the same genes, such as *APOE*, which is associated with both Alzheimer's disease and coronary artery disease (Martins, Berger, Sharman, Verdile, Fuller, & Martins, 2009). In studies examining the relation of IQ with CVD, it is commonplace to control for candidate confounding environmental factors, including socioeconomic status, but very few have examined the role of possible common genetic aetiology (Silventoinen, Posthuma, van Beijsterveldt, Bartels, & Boomsma, 2006), which we address in the present study.

The field of cognitive epidemiology focuses on cognitive test performance as a predictor of health outcomes. One very important health outcome is CVD. In a prospective study of 1145 men and women over 20 years, using the Relative Index of Inequality, IQ was the second strongest predictor of CVD mortality (showing a sex-adjusted hazard ratio of 3.76) after cigarette smoking, and before income, blood pressure and physical activity (Batty, Deary, Benzeval, & Der, 2010). The results of other, large longitudinal studies show a similar effect size for IQ on CVD mortality risk (e.g., Batty, Mortensen, Nybo Andersen, & Osler, 2005; Batty, Shipley, Mortensen, Gale, & Deary, 2008; Batty et al., 2009). Reverse causality (i.e., CVD predicting IQ) has largely been ruled out as an explanation for this association by studies in which IQ is measured in childhood or early adulthood; that is, when chronic disease is unlikely to occur (Batty, Deary, & Gottfredson, 2007). Several theories have been proposed to explain this association (Batty, Deary, & Gottfredson, 2007). One account is based on high IQ leading to adult socioeconomic advantage and therefore healthier environments, better health practices (e.g., smoking abstinence, higher levels of physical activity), improved access to healthcare services, and reduced psychiatric disease (and thus lower mortality). An alternative explanation invokes body system integrity, where high IQ reflects superior neural connections or other improved physiological system function.

At least half of the variation in cognitive abilities–especially general cognitive ability (*g*) – is due to genes, with the remainder presumed to be mostly influenced by an individual's unique environment (Deary, Spinath, & Bates, 2006). CVD and its risk factors are also influenced to some extent by genetic effects; examples of reported heritabilities are: 9% for physical activity, 46–84% for smoking traits, and 24–37% for blood pressure variables (e.g., Batra, Patkar, Berrettini, Weinstein, & Leone, 2003; Mitchell, Rainwater, Hsueh, Kennedy, Stern, & Maccluer, 2003; van Rijn et al., 2007). Therefore, the correlation between cognitive ability and CVD risk factors could be due to genes, the environment, or both. To investigate the relative contribution of genes and environment to this relationship, a genetically informative sample of individuals with cognitive data and a wide range of CVD risk factors is required. No studies have explored this using a comprehensive measurement battery, although a few studies have investigated specific CVD risk factors. For example, Silventoinen et al. (2006) used a twin design to show that genetic factors mediated the relationship between height and IQ in childhood, adolescence and middle-age. In the present study, which focuses on Generation Scotland's Scottish Family Health Study, the extended pedigree design enables statistical separation of genetic and environmental components of variance via comparison of the trait similarity between family members of known genetic relatedness (Falconer & Mackay, 1996).

Behavioural genetic studies typically employ a twins-reared-together design to estimate heritability because these cohorts are relatively easy to ascertain and the assumption of the equal environments of twins raised in the same family enables the separation of the environment into shared and unshared components. However, estimates of additive genetic variance from twin designs are biased if there is a difference in the environments of identical and non-identical twins. Maternal effects (e.g., prenatal environment) for example might differ between identical and non-identical twins, indeed they have been shown to differ between twin pairs and non-twin sibling pairs, accounting for 20% of the IQ covariance between twins and 5% between siblings (Devlin, Daniels, & Roeder, 1997; Visscher, Hill, & Wray, 2008). In this scenario, the extended pedigree design will not inflate estimates of additive genetic variance, although they too can provide biased variance estimates under certain conditions, for instance, where there are age differences in heritability; another limitation is the potential confounding of maternal genetic, shared environmental and dominance genetic effects. With respect to nuclear family designs there is less environmental confounding in the extended pedigree design due to the lower likelihood of environmental sharing between (more distant) family members, and under a polygenic model the variety of relationship pairings enables exact specification of the expected covariances (Rice, 2006); they can also provide more power than studies based solely on pairs of relatives (Williams-Blangero & Blangero, 2006).

In this study, we use an extended pedigree design to examine the associations – and to what extent these derive from genetic and environmental sources – between cognition and a series of well-established CVD risk factors (Yusuf, Reddy, Ounpuu, & Anand, 2001). They include: blood pressure (Lewington, Clarke, Qizilbash, Peto, & Collins, 2002), adiposity (Krakauer, Franklin, Kleerekoper, Karlsson, & Levine, 2004), height (Batty, Gunnel, Langenberg, Smith, Marmot, & Shipley, 2006), tobacco habit (Jacobs et al., 1999), physical activity (Lee, Paffenbarger, & Hennekens, 1997), fruit and vegetable intake (He, Nowson, Lucas, & MacGregor, 2007), heart rate (Fox et al., 2007), ankle-brachial index (Heald, Fowkes, Murray, & Price, 2006), lung function (Sin, Wu, & Man, 2005), minor psychiatric disorder (Rasul, Stansfeld, Hart, & Davey Smith, 2005), alcohol use (Gronbaek, 2002), education, and socioeconomic position (Kaplan & Keil, 1993). While our study cannot contribute directly to the debate on causality between IQ and CVD risk factors, it is important to understand whether the association relies on antecedents of a biological or environmental nature or both.

2. Methods

2.1. Identification and recruitment of participants

The study protocol has been described in detail elsewhere (Smith et al., 2006). We briefly describe approach, recruitment, and data and sample collection. Initial contact in a family (the proband) was through an invitation letter from