CORNELIUS A. RIETVELD

Essays on the Intersection of Economics and Biology

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Opstellen op het kruispunt van economie en biologie

THESIS

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Contents

Preface (Voorwoord)

Op 8 oktober 2003 bracht ik, als vierde klas middelbare school leerling, een kennismakingsbezoek aan de Erasmus Universiteit Rotterdam. Mijn verslag van deze dag meldt: 'Op de Erasmus Universiteit lijkt het studeren me leuker dan op de Universiteit Leiden. Ik vond er een heel ander sfeertje hangen, wat mij wel aanstond'. Nu, ruim tien jaar later, kan ik zeggen dat het sfeertje mij er nog steeds aanstaat. Na het behalen van mijn bachelor en master diploma aan deze universiteit, hoop ik er op 2 oktober 2014 ook te promoveren. Mijn proefschrift heeft u inmiddels in handen; laat ik u in het kort vertellen hoe dit proefschrift tot stand is gekomen.

Na het afronden van de middelbare school begon ik in 2006 aan de studie econometrie en besliskunde. Daar had ik veel plezier in en ik was daarom, ondanks een leuke afstudeerstage in het bedrijfsleven, op zoek gegaan naar een promotieplek om het verblijf aan de universiteit met nog enkele jaren te verlengen. De beschikbare promotieplekken bij econometrie gingen helaas over onderwerpen die mij niet zo aanspraken. Onverwachts ontving ik echter op 25 juni 2010 een e-mail waarin gevraagd werd of ik interesse had in een onderzoeksproject waarin 'het doel van het onderzoek is om relaties te vinden tussen medische gegevens en het al of niet ondernemer zijn'. Dat sprak mij wél aan, al begreep ik nog maar half wat het project precies inhield. Enkele dagen daarna had ik prettige ontmoetingen met leden van het onderzoeksteam en solliciteerde ik naar deze onderzoeksplek.

Op 10 juli 2010 kreeg ik te horen, via een e-mail in de kenmerkende 'Thurik-style', dat ik was gekozen als nieuwe promovendus van het project. Ik kon al snel beginnen, zelfs nog voor mijn afstuderen, door middel van een overbruggingskrediet van EIM/Panteia. Zo raakte ik betrokken bij een uitdagend onderzoeksproject, dat al in 2007 was opgestart door mijn promotoren Roy Thurik, Patrick Groenen, Albert Hofman en dagelijkse begeleider Philipp Koellinger. In het project werkten wetenschappers van de Erasmus School of Economics en het Erasmus Medisch Centrum samen, om het 'ondernemerschapsgen' te vinden. Het zou mijn taak worden de gezondheidsconsequenties te onderzoeken van een genetische aanleg voor ondernemerschap. Helaas bleek al snel dat er aan een noodzakelijke voorwaarde voor dit onderzoek, namelijk de statistische identificatie van die genetische aanleg, niet op korte termijn voldaan kon worden. Al is de hoop er nog steeds om ooit een dergelijke 'mismatch' analyse te doen, in dit proefschrift is alleen ander (wel gerelateerd) onderzoek te vinden!

Het grote doel van het promotietraject is in vier jaar een verdedigbaar proefschrift klaar te hebben. Aan het begin van het traject lijkt vier jaar hiervoor erg lang, maar de tijd vliegt voorbij kan ik wel zeggen! Ik ben daarom blij dat het gelukt is dit proefschrift én de verdediging achter de rug te hebben voordat mijn vierjarig contract als promovendus af-

loopt. Het proefschrift bevat naast een inleiding zeven hoofdstukken die afzonderlijk leesbaar zijn. Vijf daarvan zijn reeds gepubliceerd in wetenschappelijk tijdschriften, en de andere twee zijn daar al ver in het beoordelingsproces. Daarnaast zijn er zeven andere artikelen gepubliceerd, en zijn er nog een handvol manuscripten in een vergevorderd stadium van ontwikkeling. De eerste vier jaar als onderzoeker smaken wat mij betreft naar meer, en ik ben daarom blij dat ik voorlopig actief kan blijven op dit onderzoeksterrein. Tevens zijn de eerste ervaringen met les geven en het begeleiden van studenten bij het schrijven van hun scriptie ook erg positief!

Ik ben nu aangekomen bij de groep mensen die ik persoonlijk wil bedanken voor hun bijdrage aan de totstandkoming van dit proefschrift. Allereerst zijn dat mijn drie promotoren en dagelijkse begeleider. Roy, jij bent altijd bereikbaar en jouw deur staat altijd open. Ik ben je dankbaar voor je vertrouwen in mij vanaf het allereerste begin. Fijn dat bij jou de persoon centraal staat, en een paper, scriptie of proefschrift pas in tweede instantie. Patrick, via jou liepen de eerste contacten voor dit promotieproject. De open ingang bij ERIM, en je precieze manier van onderzoek hebben zeker bijgedragen aan het welslagen van dit project. Bert, jouw rol als stimulator, facilitator en contactlegger zijn cruciaal geweest voor het onderzoek in dit proefschrift. Dank daarvoor. Philipp, your enduring enthusiasm to develop a new interdisciplinary research field and your constant pursuit of scientific excellence are very stimulating. Also many thanks for the energy you put into the Social Science Genetic Association Consortium (SSGAC), the consortium which is very important for our collaborative work and for this thesis as well!

I would like to thank Han Bleichrodt, Ingmar Franken, Henning Tiemeier, André Uitterlinden, and Dinand Webbink for serving on either the inner or the plenary committees. I feel very fortunate to have such a highly qualified interdisciplinary committee. Due to the fact that I gathered more than 200 co-authors in the last four years, I cannot thank every single person whom I have worked with individually. However, I would like to mention Dan Benjamin and David Cesarini by name. As co-founders of the SSGAC and collaborators on many projects they have been very important for this thesis. Thanks for all and I hope that our collaboration remains as fruitful as it is!

Dank ook aan de leden van de vakgroep Toegepaste Economie voor de prettige werksfeer in de afgelopen jaren. In het bijzonder dank ik Brigitte, Jolanda en Peter als leden van de ondernemerschapsgroep voor het gezellige, maar ook productieve samenwerken. I would like to thank Aysu, Geertjan, Pourya, Matthijs, Ronald and Wim, the other PhD students of the entrepreneurship group, for the good time together. Matthijs, jij in het bijzonder bedankt. Als mijn voorganger heb jij mede het fundament gelegd voor dit proefschrift en dus ook de significante resultaten erin. Tevens bedank ik Anka, Gerda, Kim, Nita en Ramona voor de onmisbare secretariële ondersteuning.

Gertjan, met jou als kamergenoot heb ik een goede tijd gehad. Veel succes met het afronden van je proefschrift, en we zien elkaar vast nog wel eens onder het genot van een kopje zelfgemaakt bonenkoffie. Jelmer, het was een mooi moment toen onze gezamenlijke studietijd bekroond werd met de publicatie van de bachelor scriptie die we samen schreven. Dank voor de geregelde, gezellige contacten, en succes bij het afronden van je proefschrift. Jan, we maakten als student min of meer toevallig kennis tijdens een college filosofie. Ik denk met veel plezier terug aan onze reflecties op het leven als promovendus en 'de theologisch/wijsgerige wending die het gesprek wel eens nam'.

Ik wil ook familie en vrienden bedanken voor hun bijdrage aan, betrokkenheid op en interesse in mijn proefschrift gedurende de afgelopen vier jaar. Een aantal noem ik in het bijzonder. Voor twee van hen is een niet onbelangrijke rol weggelegd tijdens de promotieplechtigheid als paranimf. Pieter, de komst van jou en je familie naar Papendrecht heeft, kan ik wel zeggen, grote gevolgen gehad voor mij. Onze gedeelde ondernemingen als Jeugdvereniging, Dabar en leeskring kunnen we nu aanvullen met vandaag. Matthijs, fijn om zo'n getalenteerde, harde werker als broer te hebben. Succes ook met het afronden van jouw studie. Dank dat jullie me vandaag bijstaan! Kees, bedankt voor het ontwerpen van de mooie cover van dit proefschrift. Hij past precies bij de titel, en maakt het proefschrift echt af.

Ik dank mijn ouders voor hun steun, en belangstelling voor mijn werk. Dank ook voor het feit dat jullie me nooit enige prestatiedruk hebben opgelegd, maar slechts daarop wezen dat ik eenvoudig mijn best moest doen. Jullie zorgden voor een thuissituatie die me daartoe ook in staat stelden. Dank ook aan mijn aanstaande schoonouders voor hun belangstelling in mijn onderzoek. Hanneke, jij weet als geen ander wat dit proefschrift mij aan inspanning gekost heeft. Wetenschappelijk werk neem je gemakkelijk mee naar huis, en ik dank je voor je interesse en geduld als het werk veel aandacht vroeg. Met onze bruiloft op 16 oktober 2014 in het verschiet volgen de mijlpalen in ons leven elkaar snel op. Ik zie er naar uit om straks samen als getrouwd stel 'in het onderwijs te werken'.

Ten slotte. Als ik zo terugkijk op de afgelopen vier jaar, dan 'kom ik niets te kort dan dankbaarheid'. Bovenal dank ik de Heere God die mij de deze jaren de kracht gaf dit proefschrift te voltooien. Johannes Calvijn vergelijkt de wereld met een spiegel waarin hij Gods glorie, wijsheid, deugden en macht ziet oplichten. En hoewel de vergaarde kennis over de wereld in dit proefschrift ook slecht 'ten dele' is, heeft het vergaren ervan er niettemin voor gezorgd dat ik temeer met hem instem.

Papendrecht, juli 2014 Niels Rietveld

CHAPTER 1

Introduction and Conclusion

Abstract

This thesis concerns research topics in which economics and biology overlap. It contains seven essays in which individual economic choices and outcomes are connected to individual biological characteristics. The first five essays in this thesis analyze the molecular genetic architecture of three measures of economic interest: educational attainment (Chapter 2 and 3), subjective well-being (Chapter 5) and entrepreneurship (Chapter 6). Using the findings on educational attainment from Chapter 2 and 3, Chapter 4 identifies genetic correlates of cognitive performance. The final two essays focus on biological predispositions, correlates and consequences of entrepreneurship, namely health (Chapter 7), laterality (Chapter 8), and dyslexia (Chapter 8).

The introductory chapter (Chapter 1) is structured as follows: Section 1.1 is devoted to the motivation of hybrid research of economics and biology. Section 1.2 expounds the contribution of three lines of research that can be followed within *biological economics*. Section 1.3 presents the research questions employed in the thesis, along with the main results. Section 1.4 discusses the implications and relevance of the findings. A conclusion, together with an overview of the publication status of each chapter, is provided in section 1.5.

1.1 Motivation

Economics is the field of research that analyzes the production, distribution, consumption, and transfer of wealth. To produce, distribute, consume, and transfer wealth (in the form of goods and services), economic agents make choices that are in line with their preferences and the availability of resources. This thesis adopts a perspective in which individual economic choices and outcomes are connected to individual biological characteristics. Thus, this thesis contains research on the intersection of economics and biology, an interdisciplinary field that is called 'biological economics'.

Such a connection between economics and another scientific discipline is not a particularity in the history of economics. Economists have always been adept at integrating ideas and concepts from other scientific fields into their own research agenda. For example, the use of mathematical methods from the physical sciences enables the representation of economic theories in meaningful, testable hypotheses. Psychological insights in cognitive and emotional mechanisms involved in decision making have changed the view on the assumed rationality of economic agents.

Biological economics is the interdisciplinary research field in which the interaction between human biology and economics is investigated, and human beings are primarily seen as biological organisms. This biological perspective was hinted at in the past by some founding fathers of modern economics. Adam Smith (1723-1790) attributed the division of labor among people to a supposedly *innate* human 'propensity to truck, barter, and exchange' (Smith, 1937; Hirshleifer, 1978). Alfred Marshall (1842-1924) is known for his preference for biological analogies of economic phenomena: 'All sciences of life are akin to one another, and are unlike physical sciences. And therefore in the later stages of economics, when we are approaching nearly to the conditions of life, biological analogies are to be preferred to the mechanical, other things being equal' (Marshall, 1961; Hodgson, 1993).

There are many examples that show how economics and biology have mutually influenced each other through history (Hirshleifer, 1977). For example, the thoughts of the economist Thomas Malthus (1766-1834) about the limits of population size in the presence of food scarcity have led to Charles Darwin's (1809-1882) idea of evolution by natural selection in the struggle for life. In the other direction, the biological concepts of mutation and selection have been used to explain cross-temporal changes of economic agents and the economy as a whole.

The field journal *Economics and Human Biology* is published since 2003. This journal 'is devoted to the exploration of the effect of socio-economic processes on human beings as biological organisms'. The 5-year impact factor of 2.511 (2013) indicates that the articles in this journal receive considerable attention. However, many economists adopt the so-called Standard Social Science Model that assumes that the mind is a cognitive device

shaped only by culture and socialization (Van der Loos, 2013). This model implies that variation in economic behaviors and outcomes is the result of nurture (the environment) rather than nature, and the interplay of these factors. Therefore, the full breakthrough of *biological economics* still stands out.

This outstanding breakthrough is unfortunate given the promises of this interdisciplinary research field. The value of scientific research on the intersection of economics and biology is high and has at least three layers (adapted from Benjamin et al., 2012a). First, knowledge about biological predispositions to economic choices and outcomes improves our understanding of the causes and consequences of individual differences. Second, biological measures known to be associated with economic choices and outcomes could be used in (otherwise non-biological) empirical work as control variables or instrumental variables. Third, information about economic predisposition to biological states and outcomes may result in targeted interventions to prevent undesired outcomes.

To fulfill these promises two major lines of research have to be followed. First, biological predispositions to economic choices and outcomes must be identified (1st Line of Research). Second, economic predispositions to biological states and outcomes must be revealed (2nd Line of Research). These two lines of research can be taken if the direction of causality between measures is indisputable, or if statistical methods can satisfactorily solve endogeneity issues. These requirements are not always fulfilled in practice, and therefore a third line of research will be followed relatively often (3rd Line of Research): the study of mere correlates between economic and biological measures. Establishing causation is often very difficult in social science, but the study of correlations is usually a first, and necessary, step toward further causal understanding.

1.2 Contribution

There are numerous topics that can be studied on the intersection of economics and biology. This thesis only makes some contributions in the three lines of research described in the previous section. This thesis addresses with three economic measures: educational attainment, subjective well-being and entrepreneurship. It also addresses four biological measures: genes, health, laterality and dyslexia. The next seven chapters study the genetic origins of educational attainment, subjective well-being and entrepreneurship (1st Line of Research), analyze the influence of entrepreneurship on health (2nd Line of Research), and study the correlation between entrepreneurship, dyslexia and laterality (3rd Line of Research).

1.2.1 Chapters following the 1st Line of Research[1]

The 1st Line of Research identifies biological predisposition to economic choices and outcomes. In this thesis, Chapters 2-6 analyze the genetic origins of educational attainment, subjective well-being, and entrepreneurship. In addition, genetic correlates of cognitive performance are identified using educational attainment.

Many economic choices and outcomes are shown to be heritable. This means that part of the observed variation in choices and outcomes in a specific population can be explained by genetic factors. The classical method to measure heritability is a twin study. In twin studies, heritability is estimated by comparing the resemblance of monozygotic (MZ) twins to dizygotic (DZ) twins. MZs are genetically identical, but DZ twins on average only 50%. Because twins grow up in the same family, the difference in similarity of MZs and DZs can be used as measure for heritability, but this methodology requires some strong functional form and independence assumptions (Kempthorne, 1997; Plomin, DeFries, McClearn, & McGuffin, 2008) that are the subject of substantial research. However, the method is still widely used and accepted within the research community.

A significant heritability estimate does not pinpoint the exact genes underlying the choice or outcome of interest. Therefore, a deeper level of analysis is needed, namely the genome itself. The human genome consists of 23 pairs of chromosomes, with one of each pair being inherited from the mother, and the other is from the father. Each chromosome is composed of two intertwined strands of DNA, and each is composed of a sequence of nucleotide molecules. There are four distinct nucleotide molecules, which are called bases: *A* (adenine), *C* (cytosine), *T* (thymine), and *G* (guanine). The base *A* on one strand is always paired with the base *T* on the other strand, and the base *C* is always paired with the base *G*. Because the bases are strictly paired in this way, DNA is conventionally described by writing the sequence of bases for only one strand. For example, at a particular locus (i.e., position on the genome), suppose an individual has inherited the *AT* base pair from the mother and the *GC* base pair from the father. At this locus, this person's genotype would be written as *AG*.

While there are a number of ways that individuals differ from each other genetically, the most common form of genetic variation is a single nucleotide polymorphisms (SNP). SNPs are very frequent and account for approximately 90% of the common variation in the human genome (Ziegler & König, 2010). A SNP occurs when individuals differ in the base pair that occurs at a particular locus. Each of the two possible base pairs is called an allele for that SNP. The allele that is less common in the population is called the minor allele. Individuals who have inherited the same allele from each parent are called homozygous for

[1] A part of this subsection is based on Koellinger et al. (2013), a manuscript I co-authored and that forms the basis of Chapter 6.

that SNP, while individuals who inherited different alleles are called heterozygous. For each measured SNP, an individual's genotype can be coded as a 0, 1 or 2, depending on the number of minor alleles (where 0 and 2 identify the two possible types of homozygotes, and 1 identifies a heterozygote). The most commonly used nomenclature for SNPs is based on *rs*-numbers, which provide a unique name for every SNP as assigned by the National Center for Biotechnology Information (USA). Measuring, or "genotyping," SNPs is performed using specialized, array-based technology that allows fast genotyping of hundreds of thousands of SNPs per individual. Arrays containing several millions of SNPs are already available, and this number is expected to increase.

It was recently estimated that the total number of SNPs in humans is approximately 73 million, out of a total of ~3.2 billion base pairs in the human genome (National Center for Biotechnology Information, 2014). Because SNPs located close to each other are highly correlated with each other, commercial SNP arrays covering only a fraction of all existing SNPs nevertheless "tag" a large part of the genetic variation in a population. The correlation structure of SNPs is now well understood due largely to the availability of reference populations whose entire genomes have been sequenced as part of projects such as HapMap phase II (The International HapMap Consortium, 2005) or 1000 Genomes (The 1000 Genomes Project Consortium, 2010). This information can be used to impute unobserved SNPs with high accuracy. For example, imputed SNPs using the HapMap CEU reference panel typically have an average accuracy of $R^2 \approx 0.95$ in a European population (Huang et al., 2009).

SNPs can be used as covariates in regression models to investigate their explanatory power for a specific dependent variable. This approach is instrumental to identify the SNPs underlying the heritability of a phenotype (an observable characteristic). Because millions of SNPs are available for testing, stringent significance criteria have to be used in order to prevent reporting false positives. This strategy (known as the genome-wide association study (GWAS)) is used to identify SNPs associated with educational attainment (Chapter 2 and 3), cognitive performance (Chapter 4) and entrepreneurship (Chapter 6). The identification of associations between SNPs and economic choices and outcomes enables out of sample prediction and biological follow-up analyses. The latter are instrumental to better understand the biological foundations of economic choices and outcomes.

SNPs can also be used to construct a measure of relatedness between individuals in a population. This relatedness measure can be used as input in the Genomic-Relatedness-Matrix Restricted Maximum Likelihood (GREML) procedure (Yang et al., 2010) to estimate the heritability of a phenotype. The GREML method is analogous to the classical twin model, but with only the components for additive genetic variation and environmental variation (thus, without the common environment component). A great advantage is that GREML can be used to estimate heritability in population samples (no family structure is

required). The GREML method is used in Chapter 5 to estimate the heritability of subjective well-being.

1.2.2 Chapters following the 2nd Line of Research

The 2nd Line of Research analyzes economic predispositions to biological states and outcomes. Knowledge about a behavioral mechanism leading to changes in biological states may lead to targeted interventions. For example, stimulating entrepreneurship is a key objective in many countries due to its assumed contribution to economic growth. If entrepreneurship also contributes to an individual's health, this may be another incentive to encourage entrepreneurial behavior in a population.

Chapter 7 of this thesis investigates how entrepreneurship influences someone's health. It makes use of the job-demand-control model (Karasek, 1979; Karasek & Theorell, 1990; Theorell & Karasek, 1996), which emphasizes two aspects of the work environment, job control and job demand, to relate occupational characteristics to health. Job control refers to how much decision-making authority an individual has regarding when and how to perform the necessary work. Job demand refers to the experienced work intensity and workload. The mismatch between job demands and job control determines the level of occupational stress, which can influence disease incidence and longevity (Cooper & Marshall, 1976; Karasek, 1979; Cooper & Smith, 1985). The job-demand-control model thus provides a good theoretical framework to analyze the relation between entrepreneurship and health.

1.2.3 Chapters following the 3rd Line of Research

The 3rd Line of Research analyzes the correlation between economic and biological measures. Correlations provide insight into the dependency between certain measures, but no information about the direction of causality between them. Therefore, correlation studies are usually only an intermediary step in the identification of causal relationships. Often, the lack of appropriate data limits the application of advanced statistical techniques to discover the existence of causal mechanisms.

Occupational choice theory (Taylor, 1999) presumes that people decide to become entrepreneurs if their total expected utility from entrepreneurship is higher than the utility they expect to derive from their best alternative employment option. This coincides with the notion that utility is high if there is a high "person-job fit", meaning that an individual's characteristics match well with the requirements of the job. Chapter 8 analyzes within this theoretical framework whether there is a relation between entrepreneurship, dyslexia and laterality.

1.3 Research Questions and Main Results

The seven essays in this thesis answer six research questions. These questions are described in the current section, together with a description of the main results.

Research question 1: Which SNPs / genes underlie the heritability of educational attainment? (Chapter 2 and 3)

Multiple studies have shown that educational attainment is moderately heritable (Branigan, McCallum, & Freese, 2013). However, attempts to find SNPs robustly associated with educational attainment have not been successful (Martin et al., 2010; Beauchamp et al., 2011). Chapter 2 reports a genome-wide association study of educational attainment in a discovery sample of 101,069 individuals and a replication sample of 25,490 individuals. Three independent SNPs are genome-wide significant (rs9320913, rs11584700, rs4851266), and all three replicate. Estimated effects sizes are tiny ($R^2 \approx 0.02\%$), approximately 1 month of schooling per allele. A linear polygenic score from all measured SNPs accounts for ≈ 2% of the variance in both educational attainment and cognitive function. These findings provide promising candidate SNPs for follow-up work, and the effect size estimates can anchor power analyses in social-science genetics. Chapter 3 investigates whether the reported findings in Chapter 2 are not spurious results due to population stratification. It finds that the three SNPs replicate, including their effect sizes, in yet another large and independent sample. In addition, the predictive power of the polygenic scores also replicates. Throughout, we apply stringent controls for potential population stratification, a common confound in genetic-association studies. The findings show that large and therefore well-powered GWA studies can identify robust and replicable genetic associations with complex behaviors.

Research question 2: Are SNPs associated with educational attainment also associated with cognitive performance? (Chapter 4)

Cognitive performance hasa strong genetic overlap with educational attainment (Calvin et al., 2012) and is a likely endophenotype between genes and educational attainment (Chapter 2 and 3). Chapter 4 identifies SNPs associated with cognitive performance using a novel two-stage discovery methodology, which is called the "proxy phenotype" approach. First, a GWAS for educational attainment is conducted in a large sample (N = 106,736), which produces a set of 69 "education-associated SNPs" (the SNPs that reach statistical significance threshold $p < 10^{-5}$). Second, using independent samples (N = 24,189), the association of these education-associated SNPs with high-quality measures of cognitive performance is measured. The results show that: (i) in contrast to a list of SNPs obtained from the candidate-gene literature on cognitive performance, the education-associated SNPs are robustly associated with cognitive performance, and (ii) three SNPs

(rs1487441, rs7923609, rs2721173) are significantly associated with cognitive performance after correction for multiple hypothesis testing. Moreover, in an independent sample of older Americans (N = 8,652), a polygenic score derived from the education-associated SNPs is strongly associated with memory and absence of dementia.

Research question 3: Do common SNPs explain a portion of the variation in subjective well-being? (Chapter 5)

Subjective well-being is a topic of research in economics, but also in other social sciences (Easterlin, 2003; Kahneman & Deaton, 2010). Twin and family studies have found that genetic factors may account for as much as 30-40% of the variance in subjective well-being (Harris, Pedersen, Stacey, & McClearn, 1992; Lykken & Tellegen, 1996; Tellegen et al., 1988; Røysamb, Harris, Magnus, Vitterso, & Tambs, 2002; Stubbe, Posthuma, Boomsma, & De Geus, 2005; Nes, Røysamb, Tambs, Harris, & Reichborn-Kjennerus, 2006; Bartels & Boomsma, 2009; Franz et al., 2012). Chapter 5 studies the genetic contributions to subjective well-being in a pooled sample of ~11,500 unrelated, comprehensively-genotyped Swedish and Dutch individuals. The method of Yang et al. (2010) is used to estimate the fraction of variance in subjective well-being that can be explained by the cumulative additive effects of SNPs that are common in the population. Our estimates are 5-10% for single-question survey measures of subjective well-being, and 12-18% after correction for measurement error in the subjective well-being measures. The results suggest guarded optimism about the prospects of using genetic data in subjective well-being research because, while the heritability is not large, the polymorphisms that contribute to it could feasibly be discovered with a sufficiently large sample of individuals.

Research question 4: Which SNPs / genes underlie the heritability of entrepreneurship? (Chapter 6)

Entrepreneurship has been shown to be partially heritable (Nicolaou, Shane, Cherkas, Hunkin, & Spector, 2008a; Nicolaou, Shane, Cherkas, & Spector, 2008b, 2009; Nicolaou & Shane, 2009. 2010; Zhang et al., 2009, Shane, Nicolaou, Cherkas, & Spector, 2010; Van der Loos et al., 2013b), however attempts to identify specific genetic variants underlying the heritable variation of entrepreneurship have until now been unsuccessful (Nicolaou, Shane, Adi, Mangino, & Harris, 2011, Van der Loos et al., 2011, 2013b, Quaye, Nicolaou, Shane, & Mangino, 2012). Chapter 6 presents results of a genome-wide association study on serial self-employment. The study investigated 5,930 individuals from two Dutch samples and attempted to replicate the discovery results in a third, Swedish sample of 2,771 individuals. The study identifies a novel genetic polymorphism that replicates in the Swedish sample (rs3774790 in the ABHD5 gene). However, a very cautious interpretation of this finding is warranted for several reasons, including a failed attempt to replicate the

association with being self-employment at least once in an independent sample of 33,138 Europeans. Furthermore, none of the previously suggested candidate genes is significantly associated with serial self-employment or any other proxy for entrepreneurship that is tested. Thus, no credible genetic associations with entrepreneurship have been discovered yet, including the results of this study.

Research question 5: Are entrepreneurs healthier than wage-workers, and why? (Chapter 7)

Entrepreneurs are often reported to be healthier than wage workers (Tetrick, Slack, Da Silva, & Sinclair, 2000; Bradley & Roberts, 2004; Stephan & Roesler, 2010); however, the cause of this health difference is largely unknown. Chapter 7 investigates the US Health and Retirement Study to gauge the plausibility of two competing explanations for this difference: a contextual effect of self-employment on health, or a health-related selection of individuals into self-employment. Three measures for health are used: the number of health conditions, self-rated health and mental health. The main finding is that the selection of comparatively healthier individuals into self-employment accounts for the positive cross-sectional difference. The results rule out a positive contextual effect of self-employment on health, and Chapter 7 present tentative evidence that, if anything, engaging in self-employment is bad for one's health. Given the importance of the self-employed in the economy, these findings contribute to our understanding of the vitality of the labor force.

Research question 6: Are entrepreneurs more often left-handed or dyslectic than wage-workers? (Chapter 8)

The supposed creativity of left-handed (Newland, 1981) and dyslectic individuals (Everatt, Steffert, & Smythe, 1999; Denny & O'Sullivan, 2007) may fit well with an entrepreneurial career for which the development of novel and useful ideas is of fundamental importance (Ward, 2004). Dyslectic individuals may also choose entrepreneurship in the absence of other relevant employment options. There is indeed ample anecdotal evidence of (famous) left-handed and dyslectic entrepreneurs. Empirical evidence from two representative Dutch samples, however, shows that dyslectic and left-handed individuals are not more likely to be(come) entrepreneurs than non-dyslectic and right-handed individuals. Despite the numerous examples of successful left-handed and dyslectic entrepreneurs, our findings suggest that entrepreneurship is not a particularly suitable career choice for left-handed or dyslectic individuals.

1.4 Implications and Discussion

This section addresses the question of how the essays in this thesis contribute to the fulfillment of the three promises (see Section 1.1) of *biological economics*. I discuss how the findings in this thesis contribute to our knowledge about biological predispositions to economic choices and outcomes. In addition, I describe how biological measures known to be associated with economic behaviors and outcomes could be used in (otherwise non-biological) empirical work as control variables or instrumental variables, and how information about economic predispositions to biological states and outcomes may result in targeted interventions to prevent undesired outcomes.

Chapters 2-6 of this thesis analyze the complex molecular architecture of economic choices and outcomes. Although it has been known for some time that many economic choices and outcomes are heritable, no robust, replicable genetic predisposition to these choices and outcomes have been found. This thesis shows that it is possible to find such associations in a robust and replicable manner, by applying relatively crude methods in combination with statistical rigor. These results warrant further large-scale genetic association studies on economic choices and outcomes.

The discovered effect sizes of genetic variants on economic choices and outcomes are tiny. The findings in this thesis, therefore, invalidate claims about 'genetic determinism' of behavior. Not a single gene, or a small number of genes, but usually a large number of genes is responsible for the heritability of a behavioral phenotype. In addition, the results show that individual differences result from natural *and* environmental influences. Neither nature *nor* nurture, but nature *and* nurture and possibly their interplay is responsible for the studied choices and outcomes.

Although the effect sizes of individual genetic variants appear to be very small for economic choices and outcomes, polygenic scores constructed from several genetic variants appear to have non-zero predictive power. This thesis shows that it is possible to predict educational attainment amongst adults out of a sample. Two other papers to which I contributed, Ward et al. (2014) and De Zeeuw et al. (2014), show that the same polygenic score can also predict educational achievement scores and attention problems amongst children. It is likely that the predictive power of the GWAS results on educational attainment for other phenotypes will be explored further in the future.

In addition, Chapter 4 of this thesis shows how genetic variants associated with educational attainment can be used to identify genetic associations with cognitive performance, which is correlated with educational attainment both phenotypically and genotypically. The GWAS findings for economic choices and outcomes are thus relevant for the study of non-economic phenotypes, and it is likely that the so-called proxy-method will be used for other phenotypes in the future as well.

There has been interest within academia to use genetic variants as instrumental variables in statistical models. This so-called Mendelian Randomization approach has been thought to have the potential to tackle endogeneity problems in statistical models by exploiting the random assortment of genes from parents to offspring (Davey Smith & Ebrahim, 2003). Apart from the fact that genetic variant are often very weak instruments, it is currently almost impossible to rule out whether the effect of a genetic variant runs only through the endogenous variable. Therefore, it is very likely that the exclusion restriction is violated, and thus that genetic variants can be used as instrumental variables in the near future (Taylor et al., 2014). The inclusion of genetic variants or polygenic scores as control variables in an otherwise non-genetic analysis could, however, be worthwhile to reduce unobserved heterogeneity within a model. The practical relevance hinges on the explanatory power of the particular genetic variant or polygenic score.

Chapter 7 underscores the importance of distinguishing between health-related selection into an occupation, and the contextual effects of an occupation on health in explaining the health of the self-employed. The results rule out a positive contextual effect of self-employment on health, and present tentative evidence that, if anything, engaging in self-employment is bad for one's health. This chapter leaves the question about what exactly leads relatively healthy individuals to select entrepreneurship open, but it offers suggestions. Further research is clearly warranted before policy implications can be given. The non-significant association between entrepreneurship, dyslexia and laterality in Chapter 8 also warrants further research. Although popular anecdotes that entrepreneurship is a particularly good occupation for dyslectic and left-handed individuals could not be substantiated, further research may want to use multiple, more refined, measures over time to study the interplay between entrepreneurship, dyslexia and laterality.

1.5 Conclusion

Biological economics combines the strengths of both economics and biology to answer its research questions. Traditionally, economics puts much emphasis on the development of theory, the rigorous use of statistical models, and the importance of the environment. Biology is more adept to an empirical approach to scientific questions and the emphasis on structural differences between individuals. This thesis shows how a collaborative confrontation between these two fields within an interdisciplinary team yields valuable scientific knowledge.

Although the full breakthrough of *biological economics* still remains, the expected value of research on the intersection of economics and biology is argued to be high. It is reasonable to assume that the interest in *biological economics* will only grow in the coming years. The increasing collection of biological data by traditional social science studies,

as well as the implementation of social science questionnaires in medical studies, are clear indicators for this. It will keep many researchers busy to analyze all of the new data.

The work in this thesis results mainly from the ongoing collaboration between the Erasmus School of Economics and the Erasmus Medical Center. I believe that the growth of *biological economics* depends strongly on the degree of cooperation between individual economists and biologists. However, also formal structures, such as the recently founded Erasmus University Rotterdam Institute for Behavior and Biology (EURIBEB), are also needed to nurture the development of this interdisciplinary field, for example by developing specialized courses in *biological economics*.

As an overview, the publication status of each chapter of this thesis is presented in Table 1.1. Five chapters have been published or accepted for publication in international peer-reviewed journals, and two are currently under review (after a first revision). In early 2014, the CHARGE Consortium (Cohorts for Heart and Aging Research in Genomic Epidemiology) awarded me the CHARGE Tiger Award "Early Career" for some of the work included in this thesis. CHARGE is a collaboration between studies in genetic epidemiology. The Rotterdam Study, hosted at Erasmus Medical Center, plays a major role in this consortium. The prize winners of the semi-annual Golden Tiger awards were selected to highlight the work of early career investigators, substantial working group contributors, and overall service to CHARGE.

Table 1.2 lists eleven additional, complete papers to which I contributed during the writing of this thesis. Seven of them have been published, and four manuscripts are currently under review at scientific journals.

Table 1.1. Publication status of chapters.

Chapter	Title	Publication status	Reference
1	Introduction and Conclusion	-	-
2	A GWAS on Educational Attainment	Published in *Science*	Rietveld et al. (2013c)
3	Replicability and Robustness of the Results of a GWAS on Educational Attainment	Accepted for publication in *Psychological Science*	Rietveld et al. (2014a)
4	Using the Educational Attainment GWAS Results to Identify Genetic Variants Associated with Cognitive Performance	Manuscript submitted for publication	Rietveld et al. (2014b)
5	Molecular Genetics and Subjective Well-being	Published in *Proceedings of the National Academy of Sciences of the United States of America*	Rietveld et al. (2013a)
6	A GWAS on Serial Self-employment	Manuscript submitted for publication	Koellinger et al. (2013)
7	Self-employment and Health	Accepted for publication in *Health Economics*	Rietveld, Van Kippersluis, & Thurik (2014)
8	Entrepreneurship, Laterality and Dyslexia	Published in *Economics Letters*	Hessels, Rietveld, & Van der Zwan (2014)

Table 1.2. Publication status of eleven other papers to which I contributed during the writing of this thesis. The papers are ordered alphabetically on the name of author(s).

Title	Publication status	Reference
Polygenic Scores Associated with Educational Attainment in Adults Predict Educational Achievement and Attention Problems in Children	Published in *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*	De Zeeuw et al. (2014)
Heritability and the Covenant	Manuscript submitted for publication	Rietveld (2013)
Living Forever: Entrepreneurial Overconfidence at Older Ages	Manuscript submitted for publication	Rietveld, Groenen, Koellinger, Van der Loos, & Thurik (2013b)
Unhealthy Perceptions about Entrepreneurship	Manuscript submitted for publication	Rietveld, Hessels, & Van der Zwan (2014)
On Improving the Credibility of Candidate Gene Studies: A Review of Candidate Gene Studies Published in *Emotion*	Manuscript submitted for publication	Rietveld & Okbay (2014)
Religious Beliefs and Entrepreneurship among Dutch Protestants	Published in *International Journal of Entrepreneurship and Small Business*	Rietveld & Van Burg (2013)
A Tabu Search Algorithm for Application Placement in Computer Clustering	Published in *Computers & Operations Research*	Van der Gaast, Rietveld, Gabor, & Zhang (2014)
Candidate Gene Studies and the Quest for the Entrepreneurial Gene	Published in *Small Business Economics*	Van der Loos et al. (2011)
The Molecular Genetic Architecture of Self-employment	Published in *PLOS ONE*	Van der Loos et al. (2013b)
Serum Testosterone Levels in Males are not Associated with Entrepreneurial Behavior in Two Independent Observational Studies	Published in *Physiology & Behavior*	Van der Loos et al. (2013a)
Genetic Variation Associated with Differential Educational Attainment in Adults has Anticipated Associations with School Performance in Children	Published in *PLOS ONE*	Ward et al. (2014)

CHAPTER 2

A GWAS on Educational Attainment

Based on Rietveld et al. (2013c).

Abstract

A genome-wide association study of educational attainment was conducted in a discovery sample of 101,069 individuals and a replication sample of 25,490 individuals. Three independent SNPs are genome-wide significant (rs9320913, rs11584700, rs4851266), and all three replicate. Estimated effects sizes are tiny ($R^2 \approx 0.02\%$), approximately 1 month of schooling per allele. A linear polygenic score from all measured SNPs accounts for ≈ 2% of the variance in both educational attainment and cognitive function. These findings provide promising candidate SNPs for follow-up work, and the effect size estimates can anchor power analyses in social-science genetics.

2.1 Introduction

Twin and family studies suggest that a broad range of psychological traits (Plomin, DeFries, Knopik, & Neiderhiser, 2013), economic preferences (Cesarini, Dawes, Johannesson, Lichtenstein, & Wallace, 2009a; Cesarini, Johannesson, Lichtenstein, Sandewall & Wallace, 2012; Benjamin et al., 2012a), and social and economic outcomes (Taubman, 1976) are moderately heritable. Discovery of genetic variants associated with such traits may lead to insights regarding the biological pathways underlying human behavior and would constitute a firm foundation for research on gene-environment interactions that would have advantages over existing approaches (Duncan & Keller, 2011). If the predictive power of a set of genetic variants considered jointly is sufficiently large, then a "risk score" that aggregates their effects could be useful to control for genetic factors that are otherwise unobserved, or to identify populations with certain genetic propensities, for example in the context of medical intervention (Benjamin et al., 2012a).

To date, however, few if any robust associations between specific genetic variants and social-scientific outcomes have been identified, likely because existing work has relied on samples that are too small (Beauchamp et al., 2011; Ebstein, Israel, Chew, Zhong, & Knafo, 2010; Ioannidis, 2005). In this paper, we apply to a complex behavioral trait—educational attainment—an approach to gene discovery that has been successfully applied to medical and physical phenotypes (Visscher, Brown, McCarthy, & Yang, 2012a), namely meta-analyzing data from dozens of samples.

The phenotype of educational attainment is available in many samples with genotyped subjects. Educational attainment is influenced by many known environmental factors, including public policies. Educational attainment is strongly associated with social outcomes, and there is a well-documented health-education gradient (Lleras-Muney, 2005; Lager & Torssander, 2012; Psacharopoulos, 1985; Adler et al., 1994*)*. Estimates suggest that a substantial part of the variance in educational attainment is explained by genetic factors (Branigan, McCallum, & Freese, 2013). Furthermore, educational attainment is moderately correlated with other heritable characteristics (Plomin et al, 2013), including cognitive function (Deary, Strand, Smith, & Fernandes, 2007) and personality traits related to persistence and self-discipline (Heckman & Rubinstein, 2001).

2.2 Empirical Analysis

To create a harmonized measure of educational attainment, we coded study-specific measures using the International Standard Classification of Education (ISCED 1997) scale (UNESCO, 2006). We analyzed a quantitative variable defined as an individual's years of schooling (*EduYears*) and a binary variable for college completion (*College*). *College* may

be more comparable across countries, whereas *EduYears* contains more information about individual differences within countries.

A genome-wide association study (GWAS) meta-analysis was performed across 42 cohorts in the discovery phase. The overall discovery sample comprises 101,069 individuals for *EduYears* and 95,427 for *College*. Analyses were performed at the cohort level according to a pre-specified analysis plan, which restricted the sample to Caucasians (to help reduce stratification concerns). Educational attainment was measured at an age at which subjects were very likely to have completed their education (over 95% of the sample was at least 30). On average, subjects have 13.3 years of schooling, and 23.1% have a college degree. To enable pooling of GWAS results, all studies conducted analyses with data imputed to the HapMap 2 CEU (r22.b36) reference set. To guard against population stratification, the first four principal components of the genotypic data were included as controls in all the cohort-level analyses. All study-specific GWAS results were quality controlled, cross-checked, and meta-analyzed using single genomic control and a sample-size weighting scheme at three independent analysis centers.

At the cohort level, there is little evidence of general inflation of *p*-values. As in previous GWA studies of complex traits (Lango Allen et al., 2010), the Q-Q plot of the meta-analysis exhibits strong inflation. This inflation is not driven by specific cohorts and is expected for a highly polygenic phenotype even in the absence of population stratification (Yang et al., 2011b).

From the discovery phase, we identified one genome-wide significant locus (rs9320913, $p = 4.2\times10^{-9}$) and three suggestive loci (defined as $p < 10^{-6}$) for *EduYears*. For *College*, we identified two genome-wide significant loci (rs11584700, $p = 2.1\times10^{-9}$, and rs4851266, $p = 2.2\times10^{-9}$) and an additional four suggestive loci (Table 2.1). We conducted replication analyses in 12 additional, independent cohorts that became available after the completion of the discovery meta-analysis, using the same pre-specified analysis plan. For both *EduYears* and *College*, the replication sample comprises 25,490 individuals.

For each of the ten loci that reached at least suggestive significance, we brought forward for replication the SNP with the lowest *p*-value. The three genome-wide significant SNPs replicate at the Bonferroni-adjusted 5% level, with point estimates of the same sign and similar magnitude (Table 2.1). The seven loci that did not reach genome-wide significance did not replicate. We performed robustness checks to see whether the meta-analytic findings are not driven by extreme results in a small number of cohorts, by cohorts from a specific geographic region, or by a single sex. We did not find evidence for this. Given the high correlation between *EduYears* and *College*, it is unsurprising that the set of SNPs with low *p*-values exhibit considerable overlap in the two analyses.

Table 2.1. The results of the GWAS meta-analysis for the independent SNPs reaching $p < 10^{-6}$ in the discovery stage.

				Discovery stage		Replication stage		Combined stage	
Phenotype	SNP	Effective allele	Frequency	Beta/OR	*p*-value	Beta/OR	*p*-value	Beta/OR	*p*-value
EduYears	rs9320913	A	0.483	0.106	4.19×10^{-9}	0.077	0.012	0.101	3.50×10^{-10}
	rs3783006	C	0.454	0.096	2.29×10^{-7}	0.056	0.055	0.088	8.45×10^{-8}
	rs8049439	T	0.581	0.090	7.12×10^{-7}	0.065	0.026	0.086	1.15×10^{-7}
	rs13188378	A	0.878	-0.136	7.49×10^{-7}	0.091	0.914	-0.097	1.37×10^{-4}
College	rs11584700	A	0.780	0.924	2.07×10^{-9}	0.923	4.86×10^{-4}	0.924	8.24×10^{-12}
	rs4851266	T	0.396	1.069	2.20×10^{-9}	1.058	0.003	1.066	5.33×10^{-11}
	rs2054125	T	0.064	1.134	5.55×10^{-8}	1.031	0.225	1.110	2.12×10^{-7}
	rs3227	C	0.498	1.061	6.02×10^{-8}	1.012	0.280	1.050	3.24×10^{-7}
	rs4073894	A	0.207	1.070	4.41×10^{-7}	1.002	0.467	1.055	5.55×10^{-6}
	rs12640626	A	0.580	1.057	4.94×10^{-7}	1.000	0.495	1.044	7.48×10^{-6}

Note: "Frequency" refers to allele-frequency in the combined-stage meta-analysis. "Beta/OR" refers to the effect size in the *EduYears* analysis and to the Odds Ratio in the *College* analysis. The *p*-value in the replication stage was calculated from a one-sided test.

Table 2.2. Regression results of the polygenic scores (*PGSs*) on *College*, *EduYears* and *Cognitive Function* in a set of unrelated individuals of the QIMR (*N* = 3,526) and STR (*N* = 6,770) cohorts using SNPs selected from the meta-analysis excluding the QIMR and STR cohorts.

		QIMR				STR			
Phenotype (PGS)	SNPs	$< 5\times10^{-8}$	$< 5\times10^{-5}$	$< 5\times10^{-3}$	All	$< 5\times10^{-8}$	$< 5\times10^{-5}$	$< 5\times10^{-3}$	All
EduYears (*College*)	R^2 (%)	0.023	0.210	1.180	2.910	0.170	0.230	0.720	1.800
	p-value	0.370	0.007	9.1×10^{-11}	1.4×10^{-24}	6.1×10^{-4}	6.9×10^{-5}	3.1×10^{-12}	1.2×10^{-28}
EduYears (*EduYears*)	R^2 (%)	0.005	0.560	1.020	2.820	0.110	0.370	0.610	1.880
	p-value	0.689	7.6×10^{-6}	1.7×10^{-9}	7.1×10^{-24}	6.5×10^{-3}	6.4×10^{-7}	1.4×10^{-10}	1.0×10^{-29}
Cognitive Function (*College*)	R^2 (%)					0.000	0.160	0.380	2.380
	p-value					0.986	0.137	0.021	5.3×10^{-9}
Cognitive Function (*EduYears*)	R^2 (%)					0.190	0.420	0.220	2.580
	p-value					0.103	0.015	0.077	1.2×10^{-9}

Note: 'SNPs' gives the *p*-value threshold used in the *PGS* construction. Results for *Cognitive Function* are based on a sample of 1,419 individuals from STR.

The observed effect sizes of the three replicated individual SNPs are extremely small. For *EduYears*, the strongest effect identified (rs9320913) explains 0.022% of phenotypic variance in the replication sample. This R^2 corresponds to a difference of ~1 months of schooling per allele. For college completion, the SNP with the strongest estimated effect (rs11584700) has an odds ratio of 0.923 in the replication sample, equivalent to a 1.6 percentage-point difference per allele in the frequency of completing college.

We subsequently conducted a "combined stage" meta-analysis, including both the discovery and replication samples. This analysis revealed additional genome-wide significant SNPs: four for *EduYears* and three for *College*. Three of these newly genome-wide significant SNPs (rs1487441, rs11584700, rs4851264) are in linkage disequilibrium with the replicated SNPs. The remaining four are located in different loci and warrant replication attempts in future research: rs7309, rs11687170, rs1056667, and rs13401104.

2.3 Discussion

Although the effects of individual SNPs on educational attainment are tiny, many of their potential uses in social science depend on their combined explanatory power. To evaluate the combined explanatory power, we constructed a linear polygenic score (The International Schizophrenia Consortium et al., 2009) for each of our two education measures using the meta-analysis results (combining discovery and replication), excluding one cohort. We tested these scores for association with educational attainment in the excluded cohort. We constructed the scores using SNPs whose nominal *p*-values fall below a certain threshold, ranging from 5×10^{-8} (only the genome-wide significant SNPs were included) to 1 (all SNPs were included).

We replicated this procedure with the samples of the Queensland Institue of Medical Research (QIMR) and the Swedish Twin Registry (STR). These are two of the largest cohorts in the study, and both of them are family-based samples. The results suggest that educational attainment is a highly polygenic trait (Table 2.2): the amount of variance accounted for increases as the *p*-value threshold becomes less conservative (i.e., includes more SNPs). The linear polygenic score from all measured SNPs accounts for ≈ 2% ($p = 1.0\times10^{-29}$) of the variance in *EduYears* in the STR sample and ≈ 3 % ($p = 7.1\times10^{-24}$) in the QIMR sample.

To explore one of the many potential mediating endophenotypes, we examined how much the same polygenic scores (constructed to explain *EduYears* or *College*) could explain individual differences in cognitive function. While it would have been preferable to explore a richer set of mediators, this variable was available in STR, a dataset where we had access to the individual-level genotypic data. Cognitive function had been measured in a subset of males using the Swedish Enlistment Battery (Carlstedt, 2000). The estimated R^2 ≈ 2.5% ($p < 1.0\times10^{-8}$) for cognitive function is actually slightly larger than the fraction of

variance in educational attainment captured by the score in the STR sample. One possible interpretation is that some of the SNPs used to construct the score matter for education through their stronger, more direct effects on cognitive function. A mediation analysis (Table 2.3) provides tentative evidence consistent with this interpretation.

The polygenic score remains associated with educational attainment and cognitive function when only within-family genetic variation is used to account for within-family phenotypic variation (Table 2.4). Thus, these results appear robust to possible population stratification.

2.4 Conclusion

Placed in the context of the GWAS literature (Visscher et al., 2012a), our largest estimated SNP effect size of 0.02% is over an order of magnitude smaller than those observed for height and BMI: 0.4% (Lango Allen et al., 2010) and 0.3% (Speliotes et al., 2010) respectively. While our linear polygenic score for education achieves an R^2 of 2% estimated from a sample of 120,000, a score for height reached 10% estimated from a sample of 180,000 (Lango Allen et al., 2010), and a score for BMI using only the top 32 SNPs reached 1.4% (Speliotes et al., 2010). Taken together, our findings suggest that the genetic architecture of complex behavioral traits is far more diffuse than that of complex physical traits.

Table 2.3. Results of a mediation analysis on educational attainment using the polygenic scores (PGSs) from Table 2.2 and a measure of cognitive function in a set of unrelated individuals in the STR sample (*N* = 1,419).

PGS	*College*			*EduYears*		
	Coefficient	SE	*p*-value	Coefficient	SE	*p*-value
Regression of *EduYears* on *PGS*						
PGS	0.097	0.026	1.5×10^{-4}	0.116	0.025	5.8×10^{-6}
Regression of *Cognitive Function* on *PGS*						
PGS	0.146	0.027	3.9×10^{-8}	0.154	0.026	6.6×10^{-9}
Regression of *EduYears* on *PGS* + *Cognitive Function*						
PGS	0.032	0.023	1.6×10^{-1}	0.048	0.023	3.8×10^{-2}
Cognitive Function	0.446	0.023	4.6×10^{-72}	0.444	0.023	3.0×10^{-71}
Indirect effect	0.065	0.012	1.3×10^{-7}	0.068	0.012	2.9×10^{-8}

Note: All variables are standardized to *z*-scores. The indirect effect measures the extent to which *EduYears* changes when the *PGS* is held fixed and cognitive function changes to the level it would have attained had the *PGS* increased by one unit (Robins & Greenland, 1992). When *Cognitive Function* is included as a covariate, the coefficient on *PGS* declines by ~2/3 and is no longer statistically distinguishable from zero. These findings are consistent with the hypothesis that cognitive function mediates the relationship between the *PGS* and educational attainment.

Table 2.4. Within-family regression results of the polygenic scores (*PGSs*) on *College*, *EduYears* and *Cognitive Function* in the QIMR and STR cohorts using SNPs selected from the meta-analysis excluding the QIMR and STR cohorts.

		QIMR				STR				QIMR + STR			
Phenotype (PGS)	SNPs	5×10^{-8}	5×10^{-5}	5×10^{-3}	All	5×10^{-8}	5×10^{-5}	5×10^{-3}	All	5×10^{-8}	5×10^{-5}	5×10^{-3}	All
EduYears	R^2 (%)	0.110	0.037	0.210	0.100	0.055	0.000	0.230	0.370	0.017	0.003	0.220	0.310
(*College*)	*p*-value	0.419	0.648	0.279	0.443	0.216	0.878	0.012	0.001	0.455	0.739	0.006	0.001
EduYears	R^2 (%)	0.340	0.096	0.810	0.034	0.010	0.010	0.040	0.250	0.002	0.001	0.110	0.190
(*EduYears*)	*p*-value	0.165	0.459	0.031	0.660	0.669	0.563	0.290	0.009	0.791	0.846	0.065	0.011
Cognitive Function	R^2 (%)					0.410	0.410	0.130	0.110				
(*College*)	*p*-value					0.203	0.201	0.474	0.035				
Cognitive Function	R^2 (%)					0.160	0.290	0.020	0.760				
(*EduYears*)	*p*-value					0.432	0.282	0.780	0.082				

Note: 'SNPs' gives the *p*-value threshold used in the *PGS* construction. Analyses for QIMR are based on 572 full-sib pairs from independent 572 families, and analyses for STR are based on 2,774 DZ twins from 2,774 independent families. Results for *Cognitive Function* are based on a sample of 798 individuals from 399 independent families in STR.

Existing claims of "candidate gene" associations with complex social-science traits have reported widely varying effect sizes—many with R^2 values more than one hundred times larger than those we find (Benjamin et al., 2012a; Beauchamp et al., 2011). To the extent that other complex social-science phenotypes are similar to educational attainment, our estimate of 0.02% can serve as a benchmark for conducting power analyses and evaluating the plausibility of existing findings in social-science genetics.

The few GWAS studies conducted to date in social-science genetics have not found genome-wide significant SNPs that replicate consistently (e.g., de Moor et al. 2012; Benyamin et al. 2014). One common prescription is to gather better measures of the phenotypes in more environmentally homogenous samples. Our findings demonstrate the feasibility of a complementary approach: identify a phenotype that, although more distal from genetic influences, is available in a much larger sample. The genetic variants uncovered by this "proxy-phenotype" methodology can then serve as a set of empirically-based candidate genes in follow-up work, such as tests for associations with well-measured endophenotypes (e.g., personality, cognitive function), research on gene-environment interactions, or explorations of biological pathways.

In social-science genetics, researchers must be especially vigilant to avoid misinterpretations. One of the many concerns is that a genetic association will be mischaracterized as "the gene for X," encouraging misperceptions that genetically influenced phenotypes are immune to environmental intervention (for rebuttals, see Jencks (1980) and Goldberger (1979)) and misperceptions that individual SNPs have large effects. Our evidence instead points to tiny effects. Nonetheless, identifying these SNPs and constructing polygenic scores are steps toward usefully incorporating genetic data into social-science research.

CHAPTER 3

Replicability and Robustness of the Results of a GWAS on Educational Attainment

Based on Rietveld et al. (2014a).

Abstract

The genome-wide association study (GWAS) on educational attainment reported in the previous chapter identified three single-nucleotide polymorphisms (SNPs) that, despite their small effect sizes ($R^2 \approx 0.02\%$), reached genome-wide significance ($p < 5\times10^{-8}$) in a large discovery sample and replicated in an independent sample ($p < 0.05$). The study also reported associations between educational attainment and indices of SNPs called "polygenic scores". We evaluate the robustness of these findings. Study 1 finds that all three SNPs replicate in another large (N = 34,428) independent sample. We also find that the scores remain predictive ($R^2 \approx 2\%$) with stringent controls for stratification (Study 2) and in new within-family analyses (Study 3). Our results show that large and therefore well-powered GWASs can identify replicable genetic associations with behavioral traits. The small effect sizes are likely to be a major contributing explanation for the striking contrast between our results and the disappointing replication record of most candidate gene studies.

3.1 Introduction

The discovery of genetic variants associated with behavioral traits could eventually be transformative for the social sciences, but the first step is "gene discovery": identifying which genes are associated with a trait. In psychology, the standard approach is the "candidate gene study." In a candidate gene study, a small set of genetic polymorphisms is selected based on their hypothesized or known biological function, and these polymorphisms are tested for association with the trait. Most candidate gene studies are based on samples of several hundred participants and apply a significance threshold of 0.05 (for a review, see Ebstein, Israel, Chew, Zhong, & Knafo, 2010).

Despite the fact that such studies continue to be published in prominent journals, the successful replication of published genetic associations with behavioral traits is the exception, not the rule (Benjamin et al., 2012a; Hewitt, 2012). In fact, the situation is so alarming that the editor of the leading field journal *Behavior Genetics* recently issued an editorial policy on candidate gene studies of behavioral traits that began "The literature on candidate gene associations is full of reports that have not stood up to rigorous replication" and went on to say "…it now seems likely that many of the published findings of the last decade are wrong or misleading and have not contributed to real advances in knowledge" (Hewitt, 2012). *Psychological Science* has endorsed the *Behavior Genetics* policy toward candidate-gene research and adopted the same strict standards for evaluating such studies.

Why the findings from candidate gene studies of complex behaviors replicate inconsistently remains an open question, but it is commonly believed that low statistical power is a major contributing factor, and that the problem of low power is further compounded if the reported *p*-values correct for only a subset of the multiple hypotheses that were tested (Hewitt, 2012; Ioannidis, 2005). Candidate gene studies also typically cannot adequately control for the well-known problem of "population stratification": genotypes may covary with unobserved environmental factors (Hamer & Sirota, 2000). For example, individuals with shared genetic ancestry (say, from the same ethnic group or from the same ancestral region) may also be more likely to share values, cultural practices, or exposure to other unobserved environmental confounds. Population stratification can give rise to associations driven by the shared environmental factors but spuriously attributed to the shared genotype (Cardon & Palmer, 2003). A finding may be confounded by population stratification even though it successfully replicates if the population structure that caused a spurious genetic discovery is also present in the replication samples.

As a result of the methodological limitations of candidate gene studies and the dramatic decline in the cost of genotyping, a paradigm shift took place around 2005 in medical research away from candidate gene studies to what are called "genome-wide association studies" (GWAS) (McCarthy et al., 2008; Pearson & Manolio, 2008; Visscher, Brown, McCarthy, & Yang, 2012). These are hypothesis-free studies in which researchers test the

phenotype of interest for association with all of the (typically millions of) measured single-nucleotide polymorphisms (SNPs) without any prior hypotheses. Because of the large number of hypotheses tested, an association is only considered established if the SNP (i) reaches the "genome-wide significance" threshold of $p < 5\times10^{-8}$, and (ii) is subsequently successfully replicated in an independent sample at a nominal significance level of 0.05 (McCarthy et al., 2008).

Advocates of GWA studies argue that they overcome or mitigate many of the limitations of candidate gene studies. First, the large number of SNPs that are tested for association makes transparent the need to correct for multiple-hypothesis testing, which is achieved by imposing the genome-wide significance threshold of $p < 5\times10^{-8}$ (McCarthy et al., 2008). Moreover, GWA studies, as a practical matter, tend to be based on larger samples (as indeed they must be to have any hope of identifying a SNP that reaches genome-wide significance).

Second, Bayes' Rule implies that conditional on observing an association at the genome-wide significance level, the association is likely to be true even if the study had only modest statistical power to detect the association in the first place; see Benjamin et al. (2012a) for calculations.

Third, GWA data can be used to mitigate the potential confound of population stratification. In particular, it has become a common practice in GWASs to (a) estimate the first four principal components (PCs) of all the genotypes measured by the gene chip (the number four having emerged as a convention), (b) drop individuals who are genetic outliers as measured by these PCs, and then (c) include the PCs as control variables in the genetic association analysis. Intuitively, the PCs capture axes of correlation across the genome resulting from common ancestry. The PCs often have a geographic interpretation (e.g., the northwest-southeast axis of Europe), jointly pinpointing the location of the common ancestor (Price et al., 2006; Price et al., 2009). Controlling for PCs has become standard in GWA studies since Price et al. (2006) showed through simulation and empirical examples that doing so can eliminate spurious associations that are due to population structure.

There are thus many reasons to expect findings from GWA studies to replicate more consistently than findings from candidate gene studies. And experiences from the literature on complex anthropometric and medical traits suggest that GWA findings do in fact have a vastly superior replication record (Visscher et al., 2012). But do positive GWA findings from studies of complex behavioral traits similarly identify credible genetic associations that replicate consistently? And if the findings do replicate consistently, do they replicate consistently because what is being observed is a real genetic signal, or could it be that population stratification generates a spurious association in both the discovery sample and the replication sample? If GWA studies do identify credible and replicable genetic associa-

tions, then they are a promising response to the non-replicability problem in gene-discovery research in the social sciences.

Until recently, virtually all GWA studies with positive findings have been studies of anthropometric or medical traits. For this reason, it may be inappropriate to infer from the superior replication record of GWA studies of medical traits that positive findings from GWA studies of behavioral traits are going to replicate consistently. If true genetic associations with behavioral traits have smaller effect sizes than true associations with anthropometric and medical traits, then GWA studies on behavioral traits will tend to generate less reliable results because they have lower power to detect true associations. Furthermore, while the convention of controlling for four PCs may be sufficient to minimize population-stratification concerns for anthropometric and medical traits, it might not be sufficient for behavioral traits, which may be characterized by more subtle population stratification.

While earlier GWA studies of behavioral traits (Benyamin et al., 2014; de Moor et al., 2012) have largely come up empty-handed (probably due to sample sizes that afforded insufficient statistical power), a recent GWAS on educational attainment with a combined sample of over 100,000 individuals (Rietveld et al., 2013c) identified three SNPs that meet the standard criteria for establishing a GWAS association, (i) and (ii) listed above. The effect sizes of the associations identified by Rietveld et al. (2013c) are indeed small: the largest effect size corresponds to an R^2 of only approximately 0.02% (equivalent to about one month of schooling per allele). This is far smaller than the effect sizes for medical and anthropometric traits, for example, it is less than one tenth the R^2 of the largest associations discovered for height (R^2 = 0.4%; Lango Allen et al., 2010) and BMI (R^2 = 0.3%; Speliotes et al., 2010). The Rietveld et al. (2013c) results therefore can serve as a test case for the robustness of the GWA approach to behavioral traits.

We sought to investigate (a) whether the Rietveld et al. (2013c) results replicate in an independent sample with far more stringent controls for population stratification than are typically applied in GWA studies of medical and anthropometric traits, and (b) whether there is any evidence overall that the meta-analytic results are contaminated by unaccounted-for population stratification.

3.2 Study 1

Study 1 sought to replicate the three genome-wide significant SNPs identified by Rietveld et al. (2013c) in a new independent sample. The Rietveld et al. (2013c) study tested approximately J = two million SNPs for association with educational attainment by running the following regression separately for each SNP $j \in \{1, 2, ..., J\}$:

(1) $$y_i = \mu_j + \beta_j x_{ij} + \gamma_j Z_i + \varepsilon_{ij},$$

where y_i is the dependent variable (the phenotype); μ_i is a constant term; x_{ij} is the number of reference alleles (0, 1, or 2) individual i is endowed with at SNP j; β_j is the coefficient of interest; and Z_i is a vector of controls, which include age, sex, and the first four PCs of the variance-covariance matrix of the genotypic data. Rietveld et al. (2013c) studied two dependent variables: *EduYears*, a measure of the number of years of schooling completed by the individual, and *College*, a binary variable equal to one if the individual had completed a college degree or its equivalent. (The point biserial correlation between the two measures is roughly 0.8) The tests of association with *EduYears* were conducted by running the linear regressions described above, and the tests of association with *College* were conducted analogously using logistic regressions.

We sought to replicate the original associations using data provided by 23andMe, a cohort based on a sample of volunteer participants (Eriksson et al., 2010) that was not included in the Rietveld et al. (2013c) study. After applying quality-control filters and restricting to individuals of European descent who responded to a survey question about educational attainment, the sample size is N = 34,428. Because of the small effects, replication samples of this magnitude are required for adequate power. Given the sample size of 34,428, our power to replicate an association with R^2 = 0.02% at $p < 0.05$ is 75%.

We used the same regression models (1) as in Rietveld et al. (2013c), except that in our analysis, the vector of controls Z_i includes (in addition to age and sex) the first 25 PCs from the sample genotype covariance matrix—compared to only 4 PCs in Rietveld et al. (2013c)—in order to reduce potential population-stratification confounding by partialing out more of the population structure.

As shown in Table 3.1, all three SNP associations reported in Rietveld et al. (2013c) replicate at a nominal significance level of 0.05, in the same direction and with similar effect sizes as in the original report. The replication of effect sizes suggests that the additional controls for population stratification from including more than 4 PCs made little difference. As a caveat, we note that since all research participants are completely anonymous to us, we cannot rule out overlap between the 23andMe sample and the Rietveld et al. (2013c) discovery or replication sample, in which case the new results would not be fully independent from the Rietveld et al. (2013c) results. We believe, however, that such potential overlap is likely to be miniscule and is therefore unlikely to drive our replication findings.

Table 3.1. Replication in 23andMe Data.

	23andMe			Rietveld et al. (2013c) Discovery			Rietveld et al. (2013c) Replication		
College	*OR*	*S.E.*	*p*-value	*OR*	*S.E.*	*p*-value	*OR*	*S.E.*	*p*-value
rs12206087	1.035	0.018	0.050	1.049	0.011	1.06×10^{-5}	1.042	0.021	0.022
rs11584700	0.954	0.020	0.022	0.924	0.012	2.07×10^{-9}	0.923	0.022	4.86×10^{-4}
rs4851266	1.071	0.019	0.0002	1.069	0.012	2.20×10^{-9}	1.058	0.012	0.003
N		34,428			95,407-95,419			23,663-23,668	

	23andMe			Rietveld et al. (2013c) Discovery			Rietveld et al. (2013c) Replication		
EduYears	*Beta*	*S.E.*	*p*-value	*Beta*	*S.E.*	*p*-value	*Beta*	*S.E.*	*p*-value
rs12206087	0.058	0.020	0.004	0.106	0.018	4.19×10^{-9}	0.077	0.034	0.012
rs11584700	-0.053	0.025	0.032	-0.086	0.021	2.98×10^{-5}	-0.126	0.041	9.61×10^{-4}
rs4851266	0.086	0.021	5×10^{-5}	0.076	0.018	3.64×10^{-5}	0.103	0.035	0.002
N		34,428			101,048-101,061			23,523-23,573	

Note: Beta is the coefficient of interest estimated by the linear regression (1) for *EduYears*, and *OR* is the odds ratio estimated by the analogous logistic regression for *College*. The Rietveld et al. (2013c) sample sizes are given by a range because different sample sizes are available for the three SNPs. In Rietveld et al. (2013c), rs9320913 is significantly associated with *EduYears* and rs11584700 and rs4851266 with *College*. Because rs9320913 is unavailable in the 23andMe data, we use rs12206087 as a (very reliable) proxy for rs9320913 ($R^2 = 0.99$); the "rs12206087" results for Rietveld et al. (2013c) are actually the results for rs9320913.

3.3 Study 2

While Study 1 used a new dataset to replicate the three genome-wide significant SNPs reported by Rietveld et al. (2013c), Study 2 used some of the same data as in the original report to probe the robustness of Rietveld et al. (2013c)'s reported "polygenic score" results to potential confounding from population stratification. Following Purcell et al. (2009), polygenic scores are commonly constructed in the GWA literature in order to allow investigators to evaluate the joint predictive power of a large number of SNPs (possibly including SNPs whose effects are too small or estimated too imprecisely to reach genome-wide significance).

Following a common approach in the genetics literature (Purcell et al., 2009; Yang et al., 2012), Rietveld et al. (2013c) constructed a polygenic score ($\hat{g}_i$) for each individual i as equal to a weighted sum of the number of reference alleles (0, 1, or 2) across a set of SNPs, where the weights are derived from the regression coefficients from a GWAS of either *EduYears* or *College*. They then evaluated the predictive power of an individual's score $\hat{g}_i$ for the individual's educational attainment using two hold-out samples (i.e., samples excluded from the GWAS used for estimating the weights): the Swedish Twin Registry (STR) sample and the Queensland Institute of Medical Research (QIMR) sample. Although the original datasets are family-based samples, one member from each family was selected at random to be included in the analyses. In each sample (and for scores constructed using GWASs of each of *EduYears* and *College*), Rietveld et al. (2013c) tested four scores constructed from increasingly large sets of SNPs, the sets of SNPs whose GWAS associations with educational attainment fell below the respective p-value thresholds: 5×10^{-8} (i.e., only the genome-wide significant SNPs), 5×10^{-5}, 5×10^{-3}, and 1 (i.e., all SNPs). For each polygenic score $\hat{g}_i$, Rietveld et al. (2013c) examined its predictive power by running the regression:

$$EduYears_i = \mu + \beta\hat{g}_i + \gamma Z_i + \varepsilon_i, \quad (2)$$

where the dependent variable is always *EduYears* (never *College*), μ is a constant term; β is the coefficient of interest; and Z_i is a vector of controls, which include age, sex, and age×sex, but no PCs (though PCs were included as controls in the GWA analyses that generated the weights for constructing the $\hat{g}_i$'s). Rietveld et al. (2013c) found that the incremental predictive power of the score (i.e., the increase in R^2 from estimating regression (2) with the score as an independent variable relative to the R^2 without the score) was larger when more SNPs were included in the score. The score containing all SNPs, which had the largest incremental predictive power, accounted for approximately 2% of the variance across individuals in educational attainment.

To explore the robustness of original prediction findings, we re-ran these prediction analyses using two distinct methods that control more stringently for population stratification. In the first, we estimated the same regression model (2), except that we additionally included in the vector of controls the first 20 PCs as control variables. In the second, we estimated mixed linear models in place of the regression models (Kang et al., 2010). Conceptually, these models involve two steps: (i) the genome-wide data are used to estimate the degree of genetic similarity between each pair of individuals in the sample, and (ii) unlike in standard regression where the covariance of the error term (in an educational-attainment regression) between any two individuals is assumed to be zero, the covariance is fitted as an increasing linear function of the individuals' genetic similarity. In other words, to the extent that two individuals are more recently descended from a common ancestor (as very accurately measured by overall genetic similarity)—and thus are more likely be similar on unobserved environmental factors—these individuals are treated as correlated observations on the relationship between educational attainment and the score.

The results are shown in Table 3.2. The upper panel shows the results from the association analyses with the scores constructed using different *p*-value thresholds. We separately report results from the STR and QIMR samples and separately for scores constructed from weights estimated using *College* and *EduYears*. The middle and lower panels show results, respectively, from regressions with 20 PCs included as controls and from mixed linear models. Each coefficient is the estimated effect of a one-standard-deviation increase in the score.

The score has the predicted sign in all analyses and accounts for approximately 2% of the variance in educational attainment when all SNPs are used to construct the score. In STR (the larger and therefore better-powered cohort), the polygenic score is statistically significant in all scenarios, even when only genome-wide significant SNPs are included. The joint effect of the SNPs with $p < 5\times10^{-8}$ is approximately 0.1%-0.2% of variance in *EduYears* in STR. Since this polygenic score includes 3 SNPs (when constructed using *College*) or 5 SNPs (when constructed using *EduYears*), the results are roughly consistent with Rietveld et al.'s (2013c) estimate that each of the most strongly associated SNPs explains approximately 0.02% of variance in *EduYears*. Overall, there is no systematic tendency for the predictive power of the scores to change when additional controls for stratification are included.

Table 3.2. Results from Additional Prediction Analyses in the samples of QIMR (*N* = 3,544) and STR (*N* = 6,770).

			QIMR				STR			
Threshold for inclusion of SNPs in PGS			$< 5\times10^{-8}$	$< 5\times10^{-5}$	$< 5\times10^{-3}$	All SNPs	$< 5\times10^{-8}$	$< 5\times10^{-5}$	$< 5\times10^{-3}$	All SNPs
No PC Adjustment	*College*	*Beta*	0.0495	0.1502	0.3581	0.5630	0.1706	0.1984	0.3469	0.5506
		S.E.	0.0554	0.0554	0.0551	0.0545	0.0496	0.0496	0.0496	0.0492
		p-value	0.3702	0.0067	9×10^{-11}	1×10^{-24}	6×10^{-4}	7×10^{-5}	3×10^{-12}	1×10^{-28}
		ΔR^2	0.0002	0.0021	0.0118	0.0291	0.0017	0.0023	0.0072	0.018
	EduYears	*Beta*	-0.0221	0.2478	0.3326	0.5544	0.1353	0.2481	0.3194	0.5617
		S.E.	0.0554	0.0551	0.0551	0.0548	0.0496	0.0496	0.0496	0.0492
		p-value	0.6894	8×10^{-6}	2×10^{-9}	7×10^{-24}	7×10^{-3}	6×10^{-7}	1×10^{-10}	1×10^{-29}
		ΔR^2	0.0000	0.0056	0.0102	0.0282	0.0011	0.0037	0.0061	0.0188
Controlling for 20 PCs	*College*	*Beta*	0.0502	0.1617	0.3567	0.5508	0.1640	0.1968	0.3407	0.5445
		S.E.	0.0554	0.0554	0.0551	0.0548	0.0496	0.0496	0.0496	0.0492
		p-value	0.3671	4×10^{-3}	1×10^{-10}	2×10^{-23}	1×10^{-3}	8×10^{-5}	7×10^{-12}	5×10^{-28}
		ΔR^2	0.0002	0.0024	0.0117	0.0278	0.0016	0.0023	0.0069	0.0176
	EduYears	*Beta*	-0.0043	0.2604	0.3122	0.5372	0.1410	0.2423	0.3059	0.5588
		S.E.	0.0554	0.0554	0.0551	0.0548	0.0496	0.0496	0.0496	0.0492
		p-value	0.94	3×10^{-6}	2×10^{-8}	2×10^{-22}	5×10^{-3}	1×10^{-6}	8×10^{-10}	2×10^{-29}
		ΔR^2	0.0000	0.0062	0.009	0.0265	0.0012	0.0035	0.0056	0.0186
Mixed Linear Model Analysis	*College*	*Beta*	0.0538	0.1505	0.3383	0.4920	0.1697	0.1902	0.3387	0.5601
		S.E.	0.0571	0.0581	0.0574	0.0581	0.0504	0.0500	0.0500	0.0508
		p-value	0.3479	0.0096	4×10^{-9}	3×10^{-17}	8×10^{-4}	1×10^{-4}	1×10^{-11}	2×10^{-28}
		ΔR^2	0.0003	0.0021	0.0105	0.0222	0.0017	0.0022	0.0068	0.0187
	EduYears	*Beta*	-0.0083	0.2303	0.2666	0.4947	0.1410	0.2403	0.3104	0.5662
		S.E.	0.0581	0.0584	0.0561	0.0587	0.0513	0.0504	0.0500	0.0504
		p-value	0.8863	8×10^{-5}	2×10^{-6}	4×10^{-17}	6×10^{-3}	2×10^{-6}	5×10^{-10}	2×10^{-29}
		ΔR^2	0.0000	0.0049	0.0065	0.0225	0.0012	0.0034	0.0057	0.0191

Note: Beta is the effect of a one-standard-deviation increase in the polygenic score on years of schooling estimated by the linear regression model (2) (the first two panel rows) or by the mixed linear model analysis (the last panel row); if *Beta* is positive, the score predicts *EduYears* in the same direction in the replication sample as in the discovery sample. *S.E.* is the estimated standard error of *Beta*, and the *p*-value is for a two-sided test. ΔR^2 is the increase in R^2 (in units of percentage points) from estimating a model that includes the polygenic score as an independent variable relative to estimating a model that excludes it.

3.4 Study 3

The gold standard for ruling out concerns about population stratification is to show that the association holds within families. The original Rietveld et al. (2013c) study reported within-family analysis using the pooled STR and QIMR sample. For this within-family analysis, the linear polygenic score constructed using all SNPs in the GWAS of *EduYears* is strongly associated with educational attainment, and the score constructed using a *p*-value threshold of 5×10^{-3} is marginally significant. Power was too low to draw conclusions about the scores constructed using *p*-value thresholds of 5×10^{-5} and 5×10^{-8} (which contain information from fewer SNPs). The STR and QIMR analyses were based on sample sizes of 2,774 DZ twin pairs and 572 full sibling pairs, respectively.

In Study 3, we use data from an independent sample, the Framingham Heart Study (FHS), to attempt to replicate the within-family analyses of the linear polygenic scores. FHS is an epidemiological study on three generations of individuals in the Massachusetts town of Framingham that was not included in any of Rietveld et al.(2013c)'s analyses. In this sample, there are 395 families with two or more full biological siblings. Fewer SNPs are available in FHS than in STR and QIMR. Consequently, the polygenic scores in Study 3 are expected to have lower explanatory power than the analogous scores from Study 2. Our focus here is on examining, within the FHS dataset, how the estimated effect of the score is affected by restricting the analysis to within-family variation.

Our analyses proceeded in three steps. First, we applied quality controls to the data, pruned the SNPs for linkage disequilibrium, and then constructed the polygenic score using the meta-analytic results from Rietveld et al. (2013c). Second, we identified all biological full siblings. Finally, we tested the score ($\hat{g}_i$) within-family by running regressions of the following form:

$$EduYears_i = \beta\hat{g}_i + \sum_{k=1}^{K}\gamma_k X_{ik} + \varepsilon_i, \quad (3)$$

where *i* indexes individuals, *k* indexes families, and X_{ik} is an indicator variable that takes the value 1 if individual *i* belongs to family *k* and 0 otherwise. Including the "family fixed-effect" X_{ik} is equivalent (except for the resulting R^2) to running a regression after both $EduYears_i$ and the score $\hat{g}_i$ are demeaned at the family level; hence the analysis uses only the within-family variation in *EduYears* and the within-family variation in the score. To account for the non-independence of the error term among siblings, we cluster the standard errors (Liang & Zeger, 1986) at the level of the family. Since we expected to have less power for this analysis than Rietveld et al. (2013c) due to the smaller number of individuals and the smaller number of SNPs, we only ran these analyses for two scores, one constructed from all SNPs in the sample and one using a *p*-value threshold of 5×10^{-3}.

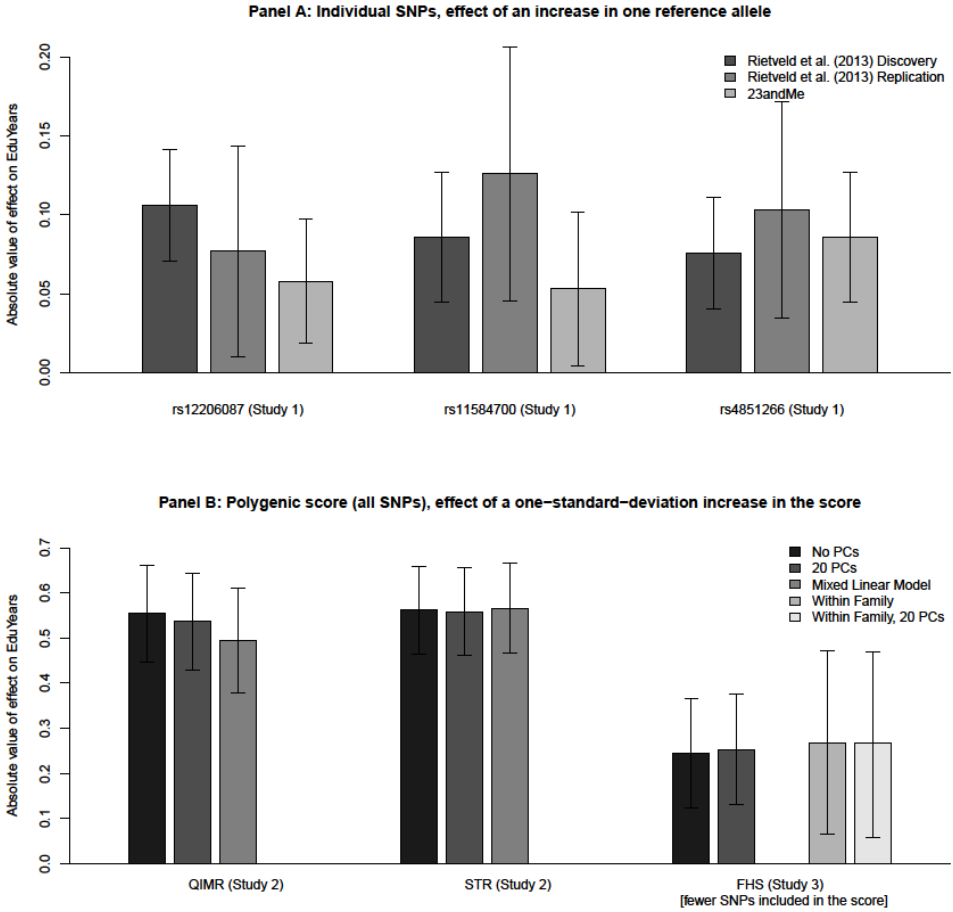
Each coefficient in Table 3.3 is the estimated effect of a one-standard-deviation increase in the score. Columns 1 and 2 report the results from the new within-family analyses using the FHS data: whether or not we control for 20 PCs, both polygenic scores constructed from all SNPs and from SNPs reaching $p < 5\times10^{-3}$ are positively and significantly associated with educational attainment. In columns 3 and 4 we also report analyses analogous to those from Study 2 (i.e., excluding the family fixed effects, thus leveraging both between- and within-family variation in the score). In these analyses, both scores are positively associated with educational attainment, again with similar results with and without the PC controls. The score from SNPs reaching $p < 5\times10^{-3}$ is marginally significant, and the score from all SNPs is highly statistically significant.

Table 3.3. Results from Analyses of Polygenic Scores for *EduYears* in FHS.

		Within-Family Variation Only		Between- and Within-Family Variation	
		(1)	(2)	(3)	(4)
Threshold for inclusion of SNPs in PGS		$< 5\times10^{-3}$	All SNPs	$< 5\times10^{-3}$	All SNPs
No PC Adjustment	*Beta*	0.2386	0.2677	0.1142	0.2448
	S.E.	0.0934	0.1034	0.0637	0.0614
	p-value	0.011	0.010	0.073	7.44×10^{-5}
	ΔR^2	0.0036	0.0037	0.0031	0.0141
Controlling for 20 PCs	*Beta*	0.2308	0.2642	0.1173	0.2534
	S.E.	0.0947	0.1044	0.0634	0.0621
	p-value	0.015	0.012	0.065	5.13×10^{-5}
	ΔR^2	0.0033	0.0036	0.0031	0.014
N, individuals		1,256		1,256	
N, families with ≥ 2 children		395		395	

Note: Beta is the effect of a one-standard-deviation increase in the polygenic score on years of schooling estimated by the linear regression model (3) (columns 1 and 2) or by linear regression model (2) (columns 3 and 4); if *Beta* is positive, the score predicts *EduYears* in the same direction in the replication sample as in the discovery sample. *S.E.* is the estimated standard error of *Beta*, and the *p*-value is for a two-sided test. ΔR^2 is the increase in R^2 (in units of percentage points) from estimating a model that includes the polygenic score as an independent variable relative to estimating a model that excludes it.

Figure 3.1. Comparison of effect sizes across studies.



Note: Panel A shows the (absolute value of the) effect on years of schooling of a change in one reference allele for each of the three individual SNPs, with 95% confidence intervals. The results are a visual representation of the numbers in Table 3.1. Panel B shows the (absolute value of the) effect on years of schooling of a change in one standard deviation of the polygenic score that includes all SNPs, with 95% confidence intervals. The results for QIMR and STR are a visual representation of the numbers in the "all SNPs" columns of Table 3.2. Similarly for the results for FHS and the "all SNPs" column of Table 3.3 (but note that the score in FHS is not comparable with the other two scores, since it is based on fewer SNPs).

3.5 Summary

To summarize, in Study 1 we replicate in an independent sample the associations between educational attainment and Rietveld et al.'s (2013c) three genome-wide significant SNPs, using more stringent controls for population stratification than is typical in the GWA literature; the next two studies show that polygenic scores robustly replicate in regressions with controls for population stratification and in within-family analyses.

To facilitate comparing the effect sizes across Studies 1-3 and Rietveld et al. (2013c)'s analyses, Figure 3.1 shows 95% confidence intervals for the effect on *EduYears*. An effect size of 0.1, for example, is approximately 1 month of schooling. For the individual SNPs, the effects are per reference allele, and for the polygenic score containing all SNPs, the effects are per one-standard-deviation increase in the score. Panel A shows that the effect sizes of the genome-wide significant SNPs are comparable across datasets. The effect sizes of the polygenic scores in Panel B are also similar in QIMR and STR across the two different datasets and methods to control for population stratification. The effect sizes of the polygenic score in FHS (Study 3) are not comparable to those from QIMR and STR; the effect sizes are attenuated in FHS because the scores are constructed from the smaller number of SNPs available in this sample. Within FHS, the effect sizes remain similar across different methods to control for population stratification, including the within-family analyses.

While these results are encouraging, we also note a potential limitation of this study. Our evidence, especially the finding that the score is significantly associated with educational attainment in within-family analyses, suggests that it is extremely unlikely that the findings of Rietveld et al. (2013c) are largely an artifact of stratification. However, biases due to very subtle population stratification may still account for some of the observed relationships between educational attainment and some of the individual SNPs. This possibility cannot be conclusively ruled out until large enough family samples are available to enable adequately powered within-family tests of association with individual SNPs. This potential limitation applies to all GWA studies. Our findings suggest, however, that the individual SNP associations with educational attainment are robust even when we include substantially more stringent controls than is standard in medical genetics.

3.6 Discussion

The contrast between the robustness of our findings and the disappointing replication record of most candidate gene studies of behavioral traits is striking. To draw the appropriate methodological conclusions, it is necessary to understand the causes of this difference.

A first major contributing factor is that the Rietveld et al. (2013c) analyses were based on a sample size that was unprecedentedly large by the standards of social-science genet-

ics. If, as now seems likely, the effects of individual genetic variants on most behavioral traits are small, much larger samples than are generally used are required to produce credible findings. This is a methodological lesson that applies to all studies whether they be GWA studies or not. However, as an empirical matter, candidate gene studies tend to be based on much smaller samples. Though it seems clear that much larger samples are needed, it is important to recognize that statistical power also depends on the reliability of the available phenotypic measure. Researchers will sometimes face a tradeoff between studying a studying a cruder variable available in a large sample (e.g., educational attainment) or more proximal variables available in a smaller sample (e.g., cognitive ability). The supplemental materials of Rietveld et al. (2013c) provide a framework for quantifying this tradeoff.

A second contributing factor is that some of the discipline that comes from the hypothesis-based research of existing candidate gene studies is illusory: because a vast majority of genes are expressed in the brain (Ramsköld, Wang, Burge, & Sandberg, 2009), it is usually possible to create an ex post rationalization for an observed association between a candidate gene and a behavioral trait that sounds at least superficially biologically plausible. Thus, the main advantage of the candidate gene approach—namely the theoretical discipline that it imposes on the investigator—may be exaggerated.

We believe there are two key implications of our findings for research on genetics of behavioral traits. First, our results suggest that standard GWAS protocols from epidemiological research can indeed be successfully applied to the study of behavioral traits and may therefore offer a way to avoid the replication failures that are plaguing much research on the genetics of complex behavior. Second, even if (given the current state of biological knowledge) current candidate-gene approaches are not bearing fruit, this does not rule out an eventual "comeback" for hypothesis-based research in the genetics of behavioral traits. In fact, we envision that as the number of credibly established associations from GWA studies rises, these discoveries will usher in a new era of "empirical candidate gene" studies in which the candidates are drawn from among the SNPs identified by GWA studies of related phenotypes. For example, the SNPs associated with educational attainment could be used as candidates to study cognitive and personality traits that may be part of the causal pathway. Such follow-up studies will of course need to be adequately powered to produce robust results, but since the GWAS results restrict the number of SNPs that are subsequently tested for association, the *p*-value threshold can be set much more liberally than the level of genome-wide significance.

What does the finding of small effect sizes—reported by Rietveld et al. (2013c) and replicated here—imply about how genetic research in psychology should be conducted and what its payoffs will be for the field? An immediate implication is that current research using genotypic data in laboratory experiments is almost certainly underpowered, and

therefore psychology should accelerate its move away from such methods, as they are unlikely to yield robust findings. A more subtle implication of the small effect sizes is that—as Turkheimer (2012) has persuasively argued—exuberant forecasts that the availability of genetic data will quickly transform the social sciences should be viewed skeptically. In principle, a genetic variant identified in an association study can explain a tiny part of the variation in the phenotype and yet point to an interesting biological system (and this has happened several times in medical genetics). In practice, it seems likely that SNPs with smaller effect sizes, on average, are more likely to operate on the phenotype through distal causal pathways involving a large number and many layers of mediating environmental factors. Therefore, it is conceivable that the identification of SNPs with very small effects will not lead to a useful psychological theory of the phenotype.

At present, it remains an open question to what extent the identification of individual SNPs will reveal new biological and psychological insights for highly polygenic behavioral traits. But we believe it is likely that genetic-association research will benefit psychology in the long run for at least two other reasons. First, even if genetic associations can only be discovered in samples of many tens of thousands of individuals, once the genetic variants to focus on have been identified, large-but-attainable samples of a few thousand individuals will provide sufficient statistical power to address interesting research questions, such as the nature and magnitude of gene-environment interactions.

Second, even though individual genetic variants have very small effects, polygenic scores can have large enough effects to be usable even in relatively small samples. The polygenic score explored here has modest explanatory power ($R^2 \approx 2\%$), but when the weights for constructing the score are estimated in larger samples, the explanatory power will be much greater. For example, Rietveld et al. (2013c) estimate that a polygenic score constructed using results from a discovery sample with $N = 500{,}000$ will have $R^2 \approx 12\%$. We anticipate that such sample sizes will be attainable in the next few years, making it possible to construct such a score. Once a polygenic score with $R^2 = 12\%$ can be calculated for each genotyped participant in a study, a sample of only 62 participants will be needed for 80% power to detect its effect.

In summary, our results suggest that in psychology, a shift away from candidate gene studies and toward GWA studies is likely to be fruitful. However, before the potential payoffs can be realized, the focus of much research on the genetics of behavioral traits will need to be reoriented, and new research infrastructures will need to be created—for example, to build much larger sample sizes than most GWA studies of behavioral traits have had access to. Nevertheless, we believe that this investment is worth making because it may lead to accumulation of reliable and replicable knowledge about the genetics of behavioral traits..

CHAPTER 4

Using the Educational Attainment GWAS Results to Identify Genetic Variants Associated with Cognitive Performance

Based on Rietveld et al. (2014b).

Abstract

We identify common genetic variants associated with cognitive performance using a two-stage approach, which we call the "proxy-phenotype method." First, we conduct a genome-wide association study of educational attainment in a large sample (N = 106,736), which produces a set of 69 "education-associated single-nucleotide polymorphisms (SNPs)." Second, using independent samples (N = 24,189), we measure the association of these education-associated SNPs with cognitive performance. Three SNPs (rs1487441, rs7923609, rs2721173) are significantly associated with cognitive performance after correction for multiple hypothesis testing. In an independent sample of older Americans (N = 8,652), we also show that a polygenic score derived from the education-associated SNPs is associated with memory and absence of dementia.

4.1 Introduction

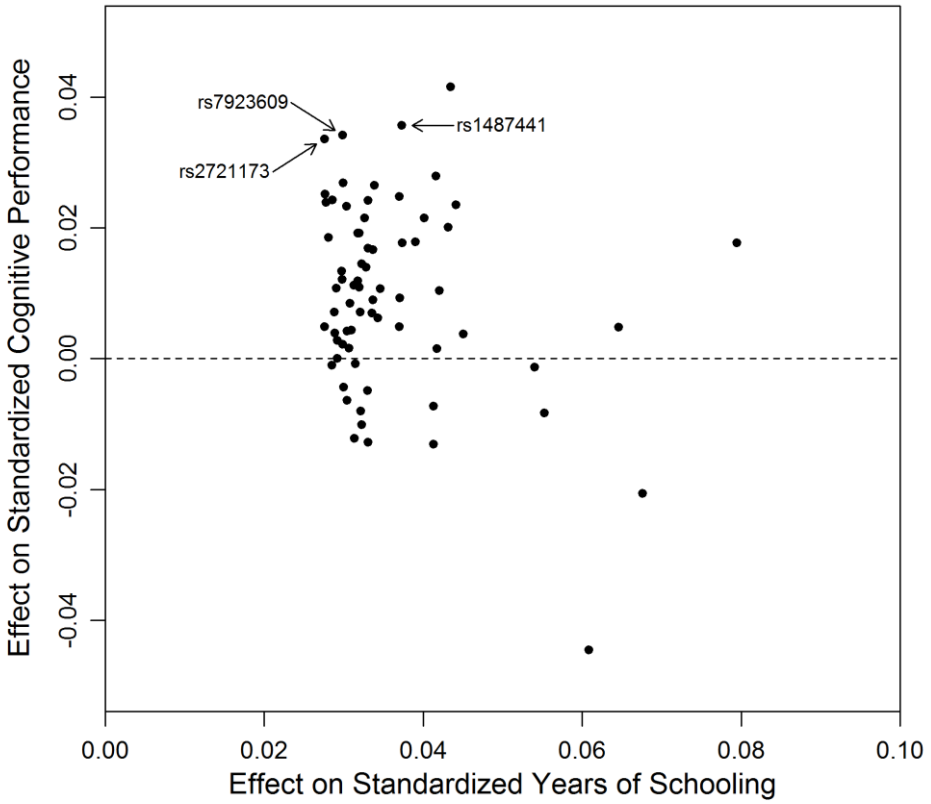
Twin and family studies have shown that at least a moderate share of variation in most facets of cognitive performance (i.e., performance by healthy individuals on cognitive tests) is associated with genetic factors (Bouchard & McGue, 2003; Plomin, DeFries, Knopik, & Neiderhiser, 2013). However, despite considerable interest and effort, research to date has largely failed to identify common genetic variants associated with cognitive performance phenotypes (Chabris et al., 2012; Benyamin et al., 2014; Davies et al., 2011), with the exception of APOE which predicts cognitive decline in older individuals (Wisdom, Callahan, & Hawkins, 2011; Lambert et al., 2013; Davies et al., 2014). Existing studies have relied on one of two research strategies. The first is a candidate-gene design, in which researchers test a small number of genetic variants for association with the phenotype of interest, typically based on hypotheses derived from the known biological functions of the candidate genes. The candidate-gene associations that have been reported with cognitive performance (Payton, 2009), however, fail to replicate when larger samples are used (Chabris et al., 2012). The second research strategy is a genome-wide association study (GWAS), in which researchers atheoretically test hundreds of thousands of single-nucleotide polymorphisms (SNPs) for association with the phenotype and apply a threshold for "genome-wide" statistical significance—typically 5×10^{-8}—in order to account for multiple-hypothesis testing. For physical and medical phenotypes, GWASs have identified many novel associations that replicate (Visscher, Brown, McCarthy, & Yang, 2012). GWASs on cognitive performance, however, have not yet identified any genome-wide-significant associations (Benyamin et al., 2014; Davies et al., 2011).

Here, we apply an alternative, two-stage research strategy, which we call the proxy-phenotype method. In the first stage, we conduct a GWAS on a "proxy phenotype" to identify a relatively small set of SNPs that are associated with the proxy phenotype. In the second stage, these SNPs serve as candidates that are tested in independent samples for association with the phenotype of interest, at a significance threshold corrected for the number of proxy-associated SNPs. In the study reported here, our phenotype of interest is cognitive performance, for which we use Spearman's measure of general cognitive ability (usually abbreviated to *g*; it is the general factor measured by a battery of diverse cognitive tests (Benyamin et al., 2014)). Our proxy phenotype is educational attainment, as measured by self-reported years of schooling.

Rietveld et al. (2013c) had suggested the strategy of using SNPs associated with educational attainment as "empirically-based candidate genes" for association with cognitive performance; here we conduct that analysis and further develop the methodology for doing so. Educational attainment is a good proxy phenotype for cognitive performance because cognitive performance is strongly genetically influenced and causally affects educational attainment, and much larger samples are available for GWAS on educational attainment.

The high genetic correlation (estimated to be roughly 0.65 or higher (Wainwright, Wright, Geffen, Luciano, & Martin, 2005; Calvin et al., 2012; Marioni et al. 2014)) between the two traits does not have straightforward implications for the statistical power to identify specific SNPs influencing cognitive performance. It does, however, imply that a polygenic score associated with educational attainment will be associated with cognitive performance; thus it may be viewed as providing an additional, suggestive justification for the approach to identifying specific SNPs.

Figure 4.1. The relationship between standardized coefficients from the first-stage regression of years of schooling on the education-associated SNPs in the Education Sample and standardized coefficients from the second-stage regression of cognitive performance on these SNPs in the Cognitive Performance Sample.



Note: The reference allele is chosen such that the coefficient on years of schooling is positive. Each point represents one of the 69 education-associated SNPs. The cloud of points is bounded away from zero effect on years of schooling because the criterion for including a SNP was its reaching $p < 10^{-5}$ in the GWAS on years of schooling in the Education Sample.

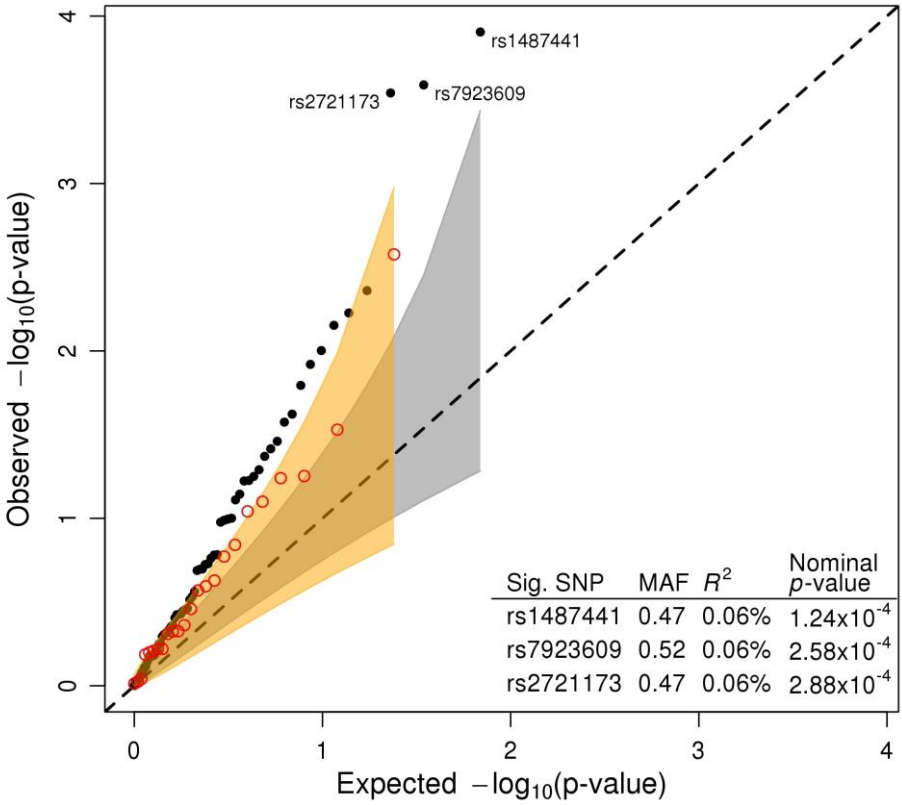
4.2 Conceptual Setup

In our first stage, we conducted a GWAS of educational attainment in a pooled "Education Sample" of 106,736 individuals. We used the same data, analysis protocol, and quantitative years-of-schooling measure as Rietveld et al. (2013c), except that we omit cohorts with high-quality measures of cognitive performance; we instead include these cohorts in the subsequent "Cognitive Performance Sample." We chose our "inclusion threshold" of $p < 10^{-5}$ for selecting candidate SNPs based on ex ante power calculations whose goal was to maximize the number of true positives among the candidates. Pruning for linkage disequilibrium the 927 SNPs that reach this threshold resulted in 69 approximately independent SNPs.

In our second stage, we tested these 69 "education-associated SNPs" for association with cognitive performance in the Cognitive Performance Sample, which comprises 24,189 genotyped subjects from 11 cohorts. The specific cognitive tests differ across cohorts, but the cognitive performance measure in every cohort is calculated as Spearman's *g*; previous research has found that *g* from different test batteries are highly correlated, especially if the batteries have many tests, or if the test is specifically constructed to measure *g* (Johnson, Bouchard, Krueger, McGue, & Gottesman, 2004; Ree & Earles, 1991; Chabris, 2007). We tested each SNP individually for association with cognitive performance using ordinary least squares, controlling for sex, age, and (depending on the cohort) at least four principal components of the genome-wide data (to reduce confounding from population stratification). At the cohort level, the analyses were conducted according to a prespecified plan. The cohorts' results were then meta-analyzed using an inverse-variance weighting scheme. Two independent teams of analysts crosschecked and verified the results.

To confirm that the education-based first stage identifies reasonable candidate SNPs for cognitive performance, Figure 4.1 plots the standardized regression coefficients from the regression of years-of-schooling on the education-associated SNPs in the Education Sample (with the reference allele chosen to ensure the coefficient is positive) against the standardized coefficients from the second-stage regression of cognitive performance on the SNPs in the Cognitive Performance Sample. The direction of the effect coincides in 53 out of 69 cases (two-sided binomial test, $p = 9.10\times10^{-6}$), indicating that this is a good context for applying the proxy-phenotype method. We were surprised that the correlation between the effect size on educational attainment and the effect size on cognitive performance is negative ($\rho = -0.25$; $p = 0.03$), although not significantly after dropping a possible outlier, the bottom-most point of the figure ($\rho = -0.14$ $p = 0.26$). A truly negative population correlation could be explained by a model wherein SNPs that affect cognitive performance more strongly tend to affect other factors that matter for educational attainment (such as personality traits) less strongly, and vice-versa.

Figure 4.2. Q–Q plot for a regression of cognitive performance on the education-associated SNPs (the dark points) with 95% confidence interval around the null hypothesis (the darkly shaded region); and Q–Q plot for a regression of cognitive performance on the theory-based SNPs (the light points) with 95% confidence interval around the null hypothesis (the lightly shaded region). The table shows the nominal effect sizes and *p*-values for the three labeled SNPs, which are the SNPs are statistically significantly associated with cognitive performance after Bonferroni correction (for testing the 69 education-associated SNPs).



To provide a benchmark for evaluating our list of education-associated candidate SNPs, we generated (via a pre-specified algorithm) a list of "theory-based" candidate SNPs for cognitive performance drawn from published findings in the candidate-gene literature. (This list does not include the SNPs comprising the *APOE* haplotype because these SNPs were not available in the cohort GWAS results.) After applying the same pruning procedure as for the education-associated SNPs, our list of theory-based SNPs contains 24 independent SNPs, of which only one is in a genomic region close to an education-associated SNP. Figure 4.2 overlays Q–Q plots for the theory-based and education-associated candidates. The education-associated candidates taken altogether are more strongly associated with cognitive performance than would be expected by chance (z =

5.98, $p = 1.12\times10^{-9}$). Whereas a visual inspection of the plot suggests that the theory-based candidates exhibit some association with cognitive performance, we cannot reject the null hypothesis for any SNP individually, nor for all of them taken together ($z = 1.19$, $p = 0.12$).

4.3 Results

The top three education-associated SNPs—rs1487441, rs7923609, and rs2721173—show clear separation from the others in Figure 4.2 and are significantly associated with cognitive performance after Bonferroni correction for multiple hypothesis testing. Consistent with the negative correlation in Figure 4.1, these SNPs are different from the three SNPs that reached genome-wide significance for association with educational attainment in the Rietveld et al. (2013c) analyses. After adjusting the SNPs' estimated effect sizes (each $R^2 \approx 0.0006$) for the winner's curse, we estimate each as $R^2 \approx 0.0002$, or in terms of coefficient magnitude, each additional reference allele for each SNP is associated with ≈0.02 standard-deviation increase in cognitive performance (or 0.3 points on the typical "IQ" scale). This $R^2 \approx 0.0002$ is about the same as the R^2 for the known SNP associations with educational attainment (Rietveld et al., 2013c) but far smaller than the largest effect sizes for complex physical traits such as height ($R^2 \approx 0.004$) and BMI ($R^2 \approx 0.003$) (Lango Allen et al., 2010;Speliotes et al., 2010).

Power calculations help shed light on why the proxy-phenotype method succeeded in identifying SNPs even though GWA studies to date on cognitive performance have not. A GWAS in our Cognitive Performance Sample of $N = 24{,}189$—which is larger than the largest GWA studies ($N = 17{,}989$ in (Benyamin et al., 2014) and $N = 3{,}511$ in (Davies et al., 2011))—would have had power 0.06% to identify a SNP whose association has $R^2 = 0.0002$. In contrast, our proxy-phenotype approach had power 12%. Given this power and the rather stringent significance threshold ($0.05/69 \approx 0.00072$), Bayesian calculations using reasonable assumptions regarding priors suggest that the posterior probabilities that these three SNPs are associated with cognitive performance are high.

Turning from specific SNPs to the set of all 69 education-associated SNPs, we assess the explanatory power of a linear polygenic score that aggregates their coefficients. In pooled results from four family-based cohorts (4,463 individuals in total), we find that the score is significantly associated with cognitive performance ($p = 8.17\times10^{-4}$), with R^2 ranging approximately from 0.2% to 0.4% across samples. Using only within-family variation, the pooled coefficient has the same sign but is smaller and has a larger standard error ($p = 0.36$). Thus we cannot rule out that some of the score's explanatory power is due to population stratification, although even without stratification, the non-significance of the within-family coefficient is not surprising given the low power of this test.

Next, we explore whether educational attainment might serve as a proxy phenotype for cognitive-health phenotypes (as opposed to cognitive performance in the normal

range). Our sample comprises 8,652 European-descent individuals over the age of 50 from the Health and Retirement Study (HRS). We confirm that, for the 60 out of 69 SNPs available in the HRS data, the direction of the effects on educational attainment generally coincides with the direction of the effects on the two cognitive-health phenotypes we study: "total word recall," which is a test for memory problems (two-sided binomial test, p = 0.01); and "total mental status," which is a battery that screens for early signs of dementia (p = 0.08). Next, we obtain the weights for a polygenic score by conducting a de novo meta-GWAS analysis of educational attainment just as in the first stage described above, but this time excluding the HRS from the Education Sample.

Figure 4.3. Coefficients from regression of standardized cognitive phenotype (Total Word Recall or Total Mental Status) on standardized polygenic score within age category, controlling for sex and clustering standard errors by individual. Error bars show ±1 standard error.

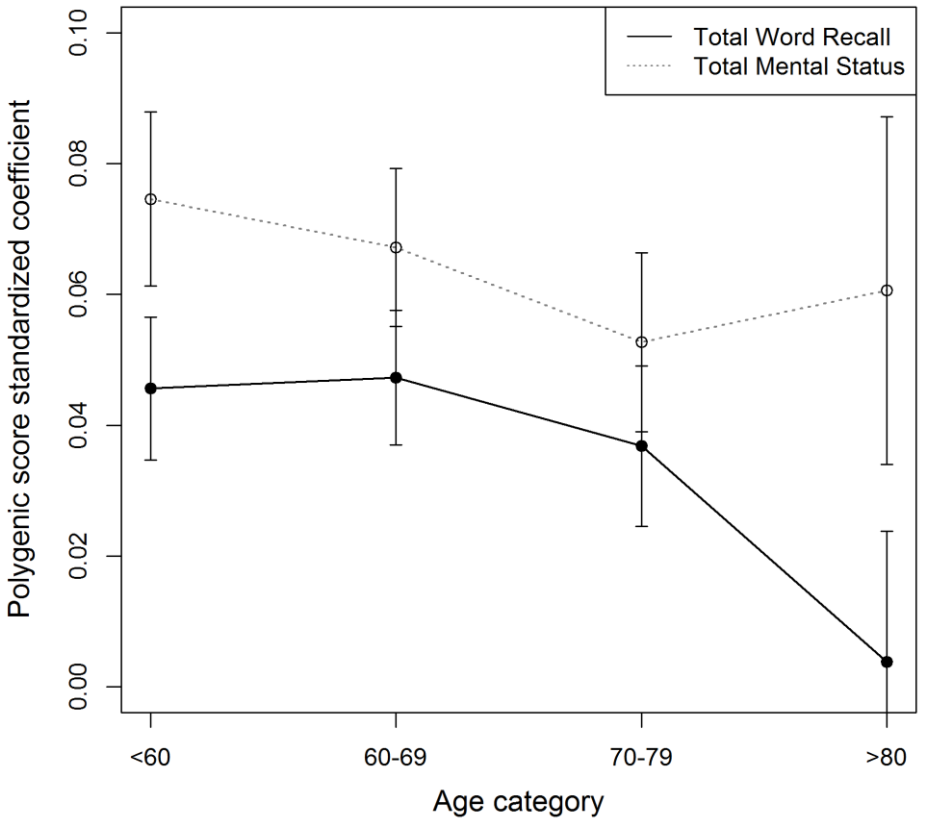


Figure 4.3 shows that the score is associated with both of the cognitive-health phenotypes. The strength of the protective effect is approximately constant across age categories from age 50 to 80, and becomes weaker for total word recall after age 80. These associations are essentially unaffected when we control for up to 20 principal components of the genome-wide data, suggesting that the associations are not driven by population stratification (Price et al., 2006). The R^2 of these associations range roughly 0.2%-0.4% (similar magnitudes as in the analysis of cognitive performance in the family-based cohorts). When we control for years of schooling, the estimated effect of the score falls roughly in half but remains statistically significant. The score is not associated with cognitive decline (i.e., the change in a cognitive phenotype across longitudinal survey waves).

4.4 Conclusion

This chapter makes two contributions. First, it demonstrates that the "proxy-phenotype method" generates positive findings in a domain in which neither candidate-gene nor GWAS approaches have so far made substantial progress. Similar approaches have sometimes been used in prior work (e.g., to find rare structural variants associated with cognition; (Stefansson et al., 2014)), and there is existing work focused on the related idea of increasing statistical power in GWAS by analyzing correlated phenotypes jointly (Ferreira & Purcell, 2009; Galesloot, Van Steen, Kiemeney, Janss, & Vermeulen, 2014).

We propose that the proxy-phenotype method, if systematically applied in social-science genetics, could be a useful complement to traditional gene discovery methods (such as GWAS) in cases where it affords greater statistical power. In the present case, it does so because (i) much larger genotyped samples are available for educational attainment than for cognitive performance, and (ii) some genetic variants are likely to be associated with educational attainment due to their more direct, stronger relationships with cognitive performance. For the same reasons, educational attainment might similarly serve as a proxy phenotype for personality traits such as persistence and self-control. In other contexts, the proxy-phenotype method may be better powered for different reasons. For example, for behavioral phenotypes with substantial measurement error—such as smoking, drinking, exercise, or eating habits—the proxy phenotype could be a medical outcome associated with the behavior (e.g., pulmonary disease for smoking, cirrhosis for alcohol consumption). We also note that, while our analysis plan specified that cohorts look up a relatively small set of education-associated SNPs in their existing GWAS results on cognitive performance, researchers with access to full GWAS results on the phenotype of interest could implement a more powerful version of the proxy-phenotype method. For example, first-stage results on the proxy phenotype could inform priors that are updated using GWAS results on the phenotype of interest.

We caution that the proxy-phenotype method (like theory-based candidate-SNP approaches) could generate an unacceptably high rate of false positives if it were applied when underpowered and if results were reported selectively. To avoid this, we propose a set of "best practices" that proxy-phenotype studies should follow: researchers should (a) conduct power calculations ex ante to justify the use of the method for a particular phenotype of interest, and report these calculations; (b) circulate an analysis plan to all cohorts prior to conducting any analysis, and register the plan in a public repository; (c) commit to publishing all findings from the study, including null results; and (d) conduct Bayesian calculations of the credibility of any findings. We followed these procedures in this paper. While replication of findings in an independent cohort would be ideal, we anticipate that it will often be infeasible given the unavailability of genotyped samples that may motivate the proxy-phenotype approach in the first place.

The second contribution of this chapter is the identification of common genetic variants associated with cognitive phenotypes. Knowing the three significant SNPs is not useful for predicting any particular individual's cognitive performance because the effect sizes are far too small, but it does enable follow-up research—e.g., pinpointing the causal variants and then conducting knock-out experiments in animals—that may ultimately shed light on biological pathways underlying cognitive variation. The polygenic scores constructed from our results may prove useful for studying gene-environment interactions. In future work, the magnitude of explained variance will increase as researchers gain access to datasets with even larger first-stage samples. Our results suggest that such scores hold promise for eventually identifying individuals whose cognitive health at older ages is at greatest risk, which could allow for appropriate preparation and (if possible) preventative intervention.

CHAPTER 5

Molecular Genetics and Subjective Well-Being

Based on Rietveld et al. (2013a).

Abstract

Subjective well-being (SWB) is a major topic of research across the social sciences. Twin and family studies have found that genetic factors may account for as much as 30-40% of the variance in SWB. Here, we study genetic contributions to SWB in a pooled sample of ~11,500 unrelated, comprehensively-genotyped Swedish and Dutch individuals. We apply a recently-developed method to estimate "common narrow heritability": the fraction of variance in SWB that can be explained by the cumulative additive effects of genetic polymorphisms that are common in the population. Our estimates are 5-10% for single-question survey measures of SWB, and 12-18% after correction for measurement error in the SWB measures. Our results suggest guarded optimism about the prospects of using genetic data in SWB research because, while the common narrow heritability is not large, the polymorphisms that contribute to it could feasibly be discovered with a sufficiently large sample of individuals.

5.1 Introduction

Subjective well-being (SWB)—most commonly measured by survey questions about a respondent's happiness or life satisfaction—is a major topic of research across the social sciences (Easterlin, 2003; Kahneman & Deaton, 2010). SWB is conceptualized to include a continuous spectrum of positive feelings and subjective life assessments (Diener, 2000; Seligman & Csikszentmihalyi, 2000; Vaillant, 2012). In contrast to standard economic indicators, which focus on consumption of material goods, responses to SWB survey questions additionally convey information regarding a broad range of other determinants of well-being, including physical and mental health, social relationships, leisure, and subjective states such as emotions and mental engagement (Diener & Seligman, 2004; Kahneman & Krueger, 2006). Because SWB measures may represent a relatively comprehensive assessment of an individual's feelings of well-being, much research aims to understand individual differences in SWB (Helliwell, Layard, & Sachs, 2012). Most of the literature examines social, economic, and psychological influences on SWB (Seligman & Csikszentmihalyi, 2000; Heady, Muffels, & Wagner, 2010), but there has also been recent interest in understanding how genetic factors influence SWB.

To date, most of these papers on the genetics of SWB are twin or family studies (Harris, Pedersen, Stacey, & McClearn, 1992; Lykken & Tellegen, 1996; Tellegen et al., 1988; Røysamb, Harris, Magnus, Vitterso, & Tambs, 2002; Stubbe, Posthuma, Boomsma, & De Geus, 2005; Nes, Røysamb, Tambs, Harris, & Reichborn-Kjennerus, 2006; Bartels & Boomsma, 2009; Franz et al., 2012). These studies draw indirect inferences about the contribution of genes to SWB by contrasting the resemblance of relatives with different degrees of environmental and genetic similarity. The literature concludes that a moderate share, typically 30-40%, of the cross-sectional variation in SWB is accounted for by variation in genes.

Recently it has become possible to directly and inexpensively assay human genetic polymorphisms, segments of DNA that differ across individuals. For medical geneticists studying health outcomes, the availability of such data has ushered in a new era, as researchers are discovering an ever-increasing number of polymorphisms related to diseases and physical traits (Visscher, Brown, McCarthy, & Yang, 2012a).

So far, however, the few attempts to find genetic polymorphisms associated with SWB have been unsuccessful (see Bartels et al. (2010) for the earliest effort we know of). One study reported an association (De Neve, 2011), but follow-up work on an augmented sample from the same data did not replicate the finding (De Neve, Christakis, Fowler, & Frey, 2012). This lack of success is not surprising, given the lessons that have emerged from genetics research across a range of medical and social-science traits. Among the central challenges for complex traits, such as height and probably even more so SWB, is that the heritability of these traits appears to be comprised of a huge number of tiny genetic effects.

Consequently, large samples of individuals—several orders of magnitude larger than those used to date in gene-discovery work in the social sciences—are needed for adequate statistical power to identify specific genetic polymorphisms (Benjamin et al., 2012a; 2012b).

Nevertheless, anticipating that polymorphisms related to SWB will soon be discovered, SWB researchers have expressed excitement about the transformative potential of genetic data for social-science research (De Neve, Christakis, Fowler, & Frey, 2012), which complements what can be learned from twin and family studies (Benjamin et al., 2012a, 2012b; Beauchamp, 2011). Most directly, knowing the functions of the relevant genes could shed light on the biological pathways that matter for SWB. If a set of polymorphisms were found to be sufficiently predictive, then they could be used in social science research as control variables. More speculatively, such polymorphisms could be used as instrumental variables (Davey-Smith & Ebrahim, 2003; Ding, Lehrer, Rosenquist, & Audrian-McGovern, 2009), in effect treating the Mendelian randomization that occurs at conception as a natural experiment to learn about the causal effects of SWB (which may be especially credible when used in family samples (Fletcher & Lehrer, 2011); for a critical perspective, see Conley (2009)). Finally, the discovery of polymorphisms associated with SWB could catalyze the study of how genetic sources of individual differences are amplified or dampened by environmental factors—and, conversely, how environmental effects are modulated by genetic pathways.

For evaluating the extent to which these promises of genetic data can be realized, a critical question is: how much of the variation in SWB will eventually be predictable using molecular genetic data? In this paper, we provide novel empirical evidence on a quantity—the "common narrow heritability," explained below—that may help calibrate reasonable expectations about the answer to this question. We also discuss the inferences that can and cannot legitimately be drawn from this estimate as well as from heritability estimates in general. For example, we scrutinize the logical coherence of invoking estimates of a trait's heritability to draw conclusions about its responsiveness to environmental interventions.

The estimates of 30-40% mentioned above likely overstate the amount of predictive power that can be obtained from molecular genetic data for two distinct reasons. First, the numbers refer to what is known as "broad heritability," but "narrow heritability" is more germane and is necessarily smaller. Narrow heritability is the fraction of variance that can be accounted for in aggregate by the cumulative additive effects of all genetic polymorphisms. It can be understood as the R^2 from a population regression of SWB on its best linear genetic predictor, i.e., a predictor in which each polymorphism enters additively, and the effect of each polymorphism is constrained to be linear in the number of reference alleles. Broad heritability, which is necessarily larger, is the fraction of variance in SWB that can be explained in aggregate by *all* genetic factors. Broad heritability can be understood as the R^2 from a population regression of SWB on its best genetic predictor, allowing

not only for linear and additive effects but also for interactions among different polymorphisms ("epistasis") and non-linear effects of specific polymorphisms ("dominance"). In a seminal paper drawing together evidence from various twin and family comparisons, Lykken (1982) proposed that for SWB (along with several other traits including personality), most, if not all, of the genetic influences stem from higher-order epistatic interactions among genetic polymorphisms. Lykken called this phenomenon the "emergenesis hypothesis" (for a recent and related discussion, see Zuk, Hechter, Sunyaev, & Lander (2012)). If true, then the narrow heritability of SWB is *much* smaller than its broad heritability. Several recent, large-scale, twin-family studies, including both twin and sibling pairs, have indeed documented evidence for the importance of both additive and non-additive genetic effects in explaining individual differences in SWB (Stubbe et al., 2005; Bartels & Boomsma, 2009).

Narrow heritability is more relevant than broad heritability for evaluating the predictive power that will be attainable using molecular genetic data because most interaction effects between polymorphisms are going to be extremely challenging to pinpoint. For genetically complex traits, we are not aware of a credible method for restricting the set of hypotheses about epistatic interactions that could be postulated. The number of possible combinations of polymorphisms that could be tested is therefore staggering, and this multiple hypothesis testing, in turn, necessitates imposing extremely stringent *p*-value thresholds. For a given sample and *p*-value threshold corrected for multiple testing, detecting even two polymorphisms whose interaction explains a given fraction of variance would require a sample size several orders of magnitude larger than the sample required to detect a single polymorphism that accounts for the same fraction of variance. As the order of the interaction increases, the requisite sample size quickly outstrips the number of people on the planet.

Second, even narrow heritability is likely to overstate the fraction of variance that *discoverable* polymorphisms are likely to capture. Estimates of narrow heritability from twin-family studies include additive variance attributable to any polymorphism, regardless of whether the polymorphism is common or rare among individuals. But individual polymorphisms related to SWB that are rare in the population—which may collectively contribute much of the narrow heritability—will be much more difficult to reliably detect than polymorphisms that are common in the population.

In our empirical analysis, we estimate a parameter that cannot be estimated from twin or family data and that is necessarily smaller than narrow heritability, namely common narrow heritability: the fraction of variance that can be accounted for in aggregate by the cumulative additive effects of genetic polymorphisms that are common in the population. To do so, we use a recently-developed method (Yang et al., 2010, Yang, Lee, Goddard, & Visscher, 2011a) called Genomic-Relatedness-Matrix Restricted Maximum Likelihood, or

GREML. We apply GREML to SWB, pooling data from two large datasets, TwinGene (TG; the genotyped subsample of the Swedish Twin Registry (Lichtenstein et al., 2006)) and the Rotterdam Study (Hofman et al., 2011), both datasets in which dense single-nucleotide polymorphism (SNP) genetic data have been collected. GREML has previously been used to estimate the common narrow heritability of height (Yang et al., 2010), intelligence (Davies et al., 2011; Chabris et al., 2012), personality traits (Vinkhuyzen et al., 2012), several common diseases (Lee, Wray, Goddard, & Visscher, 2011), schizophrenia (Lee et al., 2012), economic and political preferences (Benjamin et al., 2012b), as well as smoking, glucose levels, and depression (Lubke et al., 2012). GREML has not previously been applied to SWB.

GREML estimates a heritability parameter by examining how, across pairs of individuals, phenotypic similarity relates to genetic similarity, after controlling for observables (in our case: age, sex, 20 principal components of the variance-covariance matrix of the genotypic data, and an indicator for dataset). However, unlike in twin-family studies, where *expected* genetic similarity (inferred from the family pedigree) is used, GREML proceeds by first estimating the *realized* genetic similarity between pairs of unrelated individuals using the dense SNP data. To be more precise, realized genetic similarity is estimated using the sample covariance matrix of the individuals' genotypes. Since the genotypic data contains over half a million SNPs, this matrix is estimated very precisely. Because the covariance is a linear operator, the GREML method picks up the fraction of variance explained by the linear, additive action of the SNPs—i.e., the part of narrow heritability that is due to the measured polymorphisms. Hence GREML does not require the assumptions—about the degree of environmental and genetic resemblance between relatives and about the specific form of genetic effects (e.g., additive or dominance)—that tend to incite controversy when twin or family data is used to estimate narrow heritability. Because the current genotyping platforms from which our dense SNP data are obtained do not measure polymorphisms that are rare but *do* tag most of the genetic variation that is common in the population (Barrett & Cardon, 2006), GREML as applied to these genotypic data yields an estimate of common narrow heritability.

The key identifying assumption in GREML is that genetic similarity is uncorrelated with similarity in uncontrolled-for environmental factors that are exogenous to genotype (as defined by Jencks (1980)). This assumption might be violated if the sample includes members of a shared extended family, such as siblings or close cousins. Therefore it is standard to include in the sample only one individual from each family (in our case, one twin from a pair) and to drop individuals whose estimated genetic relatedness lies outside a small interval around zero. Since there is more random variation in the realized degree of genome sharing relative to the expected degree as the expected relatedness declines (Hill & Weir, 2011), uncontrolled-for environmental confounding factors are less likely to drive

estimates that are based on realized relatedness among individuals whose expected relatedness is negligible.

We measure SWB in the TG and RS samples using responses to the two items from the Center for Epidemiologic Studies Depression Scale (CES-D) positive affect subscale that are available in both studies, namely responses regarding how frequently "*During the past week, I was happy*" and "*During the past week, I enjoyed life.*" We refer to these questions, respectively, as *Happy* and *Enjoy*. Responses are elicited using a four-point Likert scale ranging from "Rarely or none of the time (less than 1 day)" to "Most or all of the time (5-7 days)." *Combined* is a composite measure of the two variables. Because a substantial majority of responses to *Happy* and *Enjoy* are either in the highest-frequency category or the second-highest category (as is common with SWB survey measures), and because the software GCTA (Yang, Lee, Goddard, & Visscher, 2011a) that we use for the GREML analysis cannot presently handle multinomial variables, we converted the responses to binary variables.

5.2 Materials and Methods

Our study combines data from the Swedish Twin Registry (STR) and the Rotterdam Study (RS). STR is a large, population-based twin registry. Between 1998 and 2002, STR administered to twins born in 1958 or earlier a survey called the Screening Across the Lifespan Twin study (SALT; Lichtenstein et al., 2006). A subsample of SALT was recently genotyped using the Illumina HumanOmniExpress BeadChip technology as part of the TwinGene project (Benjamin et al., 2012b). We refer to these ~10,000 genotyped SALT respondents as the "TG" sample. TG participants are all born between 1911 and 1958.

RS is a large, population-based prospective cohort study of elderly people ongoing since 1990 in the city of Rotterdam in the Netherlands (Hofman et al., 2011). ~11,000 subjects in RS have been genotyped using the Illumina 550K and 610K arrays. RS respondents are divided into three cohorts, which we refer to as RS-I, RS-II, and RS-III.

To minimize the expected relatedness of the individuals in our sample, we only included one twin per family in the TG sample. If only one twin from a pair had answered both survey questions, the individual with complete phenotypic data was included in the analysis. If both twins had complete phenotypic data, one of them was chosen at random. We then pooled the resulting sample with the RS sample and used the GCTA software to estimate the pairwise relatedness between all individuals in the pooled dataset. Following convention, we restricted the sample to individuals whose pairwise relatedness did not exceed 0.025 in absolute value.

Table 5.1. Distribution of single-question SWB measures.

SWB measure	Sample	*N*	% Rarely or none of the time (less than 1 day)	% Some or a little of the time (1-2 days)	% Occasionally or a moderate amount of time (3-4 days)	% Most or all of the time (5-7 days)
Happy	RS-I	3,842	7.0	7.7	15.9	69.5
	RS-II	2,075	4.5	11.0	22.3	62.2
	RS-III	2,992	2.9	9.8	20.3	67.1
	TG	6,675	5.1	11.0	44.9	39.0
	RS+TG	15,584	5.1	10.0	30.0	55.0
Enjoy	RS-I	3,866	6.1	7.0	13.3	73.6
	RS-II	2,080	4.2	10.3	17.9	67.6
	RS-III	2,990	2.6	8.7	15.7	72.9
	TG	6,751	2.4	3.7	27.0	66.9
	RS+TG	15,687	3.6	6.3	20.3	69.8

Note: RS: Rotterdam Study. TG: Swedish Twin Registry TwinGene sample.

Table 5.2. Distribution of combined SWB measures.

SWB measure	Sample	*N*	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)
Combined	RS-I	3,830	3.2	2.1	5.0	6.4	8.2	11.5	63.5
	RS-II	2,070	2.7	1.7	6.4	6.3	12.0	15.9	55.1
	RS-III	2,989	1.4	1.4	5.2	5.8	11.0	14.3	61.0
	TG	6,659	1.1	1.3	3.8	8.0	21.4	28.7	35.8
	RS+TG	15,548	1.9	1.6	4.7	6.9	14.9	20.0	50.0

Note: RS: Rotterdam Study. TG: Swedish Twin Registry TwinGene sample.

These restrictions brought the sample size to just below 6,000 individuals in each sample. Our analysis is restricted to individuals with SNP data that passed quality controls and who answered both questions. Results in TG are based on 627,011 SNPs; in RS, on 533,323. Due to incomplete overlap in the two samples, the number of SNPs in the pooled sample is larger, 852,597.

To convert the *Happy* and *Enjoy* to binary variables, we coded responses as "high" if they were the highest-frequency category and "not high" otherwise. We also constructed a composite measure of the two variables, which we call *Combined*, whose value is "high" if both *Happy* and *Enjoy* are high and "not high" otherwise. By generating the binary variables in this way, the fraction coded as high (or equivalently, not high) is made as close as possible to one half, thereby maximizing the variance and hence statistical power. The distributions of SWB measures before they were binarized are given in Table 5.1 and Table 5.2.

In the analyses we assume that each binary variable we observe results from the realization of an underlying, normally-distributed random variable for liability falling above or below some threshold. Table 5.3 reports age and sex, as well as the fraction of individuals coded as high for the three variables. Throughout, we control for sex, age, age squared, dummies for each of the three RS cohorts (TG is the omitted category), and, to guard against population stratification, the first 20 principal components (PCs) of the genotype data.

5.3 Results

Table 5.4 reports the GREML estimates. For each sample, TG and RS, we report the fraction of variance explained by the measured SNPs for each of the two questions and for the combined SWB measure. We also report estimates with the TG and RS results pooled. In the TG sample, the GREML estimate for *Happy* is 0.10 (s.e. 0.10); for *Enjoy*, 0.06 (s.e. 0.10); and for *Combined*, 0.08 (s.e. 0.10). The corresponding figures in RS are 0.06 (s.e. 0.10), 0.04 (s.e. 0.10), and 0.08 (s.e. 0.10). The estimates in the pooled sample are of course more precise. For two out of the three SWB measures, *Happy* ($h^2_{\text{SNP}} = 0.10$; s.e. 0.05), and *Combined* ($h^2_{\text{SNP}} = 0.09$; s.e. 0.05), the estimates are statistically distinguishable from zero at the 5% level.

Table 5.3. Descriptive Statistics GREML analysis samples.

Sample	*N*	%Female	Mean age (s.d.)	*N Happy* (%high)	*N Enjoy* (%high)	*N Combined* (%high)
RS-I	3,878	58.6%	72.42 (7.35)	3,842 (69.5%)	3,866 (73.6%)	3,830 (63.5%)
RS-II	2,085	54.3%	64.72 (7.93)	2,075 (62.2%)	2,080 (67.5%)	2,070 (55.1%)
RS-III	2,993	56.3%	57.03 (6.78)	2,992 (67.0%)	2,990 (72.9%)	2,989 (60.1%)
RS	8,956	56.8%	65.48 (9.91)	8,909 (67.0%)	8,936 (72.0%)	8,889 (60.7%)
TG	6,767	52.6%	67.59 (8.92)	6,675 (38.9%)	6,751 (66.9%)	6,659 (35.8%)
RS+TG	15,723	55.0%	66.39 (9.35)	15,584 (55.0%)	15,687 (69.8%)	15,548 (50.0%)

Note: RS: Rotterdam Study. TG: Swedish Twin Registry's TwinGene sample. For the GREML analysis in the TG sample one member per family is used. "*N Happy*" refers to the number of observation individuals with non-missing data for *Happy*; analogously for "*N Enjoy*" and "*N Combined*." For *Happy* and *Enjoy*, "%high" refers to the fraction of individuals who chose the highest response category for the SWB question; for *Combined*, it is the fraction coded as high for both questions.

Table 5.4. GREML (common narrow heritability) estimates for SWB.

		Happy ("...I was happy)"				*Enjoy* ("…I enjoyed life")				*Combined*			
Sample	#SNPs	*N*	h^2_{SNP}	s.e.	*p*	*N*	h^2_{SNP}	s.e.	*p*	*N*	h^2_{SNP}	s.e.	*p*
RS	533,323	5,904	0.06	0.10	0.28	5,919	0.04	0.10	0.35	5,893	0.08	0.10	0.20
TG	627,011	5,682	0.10	0.10	0.16	5,742	0.06	0.10	0.28	5,670	0.08	0.10	0.22
RS+TG	852,597	11,484	0.10	0.05	0.01	11,558	0.05	0.05	0.19	11,461	0.09	0.05	0.03

	N	ρ	s.e.	*N*	ρ	s.e.	*N*	ρ	s.e.
SALT Retest	105	0.55	0.12	105	0.41	0.15	105	0.61	0.12
RS Retest	7,845	0.41	0.03	7,916	0.42	0.03	7,795	0.39	0.03

Note: "RS" is the three Rotterdam cohorts pooled together. "TG" is the Swedish Twin Registry TwinGene sample. We estimated the matrix of genetic relatedness after omitting one twin per pair in the Swedish data and then restricted the analyses to individuals whose relatedness did not exceed 0.025. *N* is the number of individuals used in the analyses after the relatedness threshold has been applied. In all analyses we control for sex, age, age squared, and the first 20 principal components of the variance-covariance matrix of the genotypic data. The *p*-value is from a likelihood ratio test of the null hypothesis that the fraction of variance explained is equal to zero. "SALT Retest" is the sample of respondents in the Screening Across the Lifespan Twin study who answered the survey twice (with one week between survey occasions). "RS Retest'' is the retest correlation estimated using RS participants who answered the relevant questions in at least two different survey waves. These answers are at least two years apart in time

These estimates are attenuated by measurement error in SWB. Moreover, because our measures of SWB are based on only two questions, the attenuation is probably more severe compared to what is typically observed for lengthier personality batteries. We estimated reliability using data on 105 SALT respondents who answered the SALT survey twice, with two weeks between the measurement occasions. Our estimates are 0.55 (s.e. 0.12), 0.41 (s.e. 0.15), and 0.61 (s.e. 0.12) for *Happy*, *Enjoy*, and *Combined*, respectively. While there are also individuals in the RS study who participated in multiple waves and for whom two or more responses are available, these responses are at least two years apart in time, and thus more of the change in measured SWB is likely to reflect true changes in SWB; nonetheless, for completeness, we also report the RS estimates in Table 5.4.

A simple adjustment for attenuation is to divide the heritability by the retest reliability. This adjustment assumes that any change in measured SWB between one survey occasion and the next is due to classical measurement error (which is uncorrelated with genotype) and not true change. Using this adjustment and the SALT retest reliabilities, we estimate that 18%, 12%, and 15% of the variance in *Happy*, *Enjoy*, and *Combined* would be accounted for by common SNPs if the SWB variables were measured without error.

5.4 Discussion and Conclusion

In this paper we provide evidence on the common narrow heritability of SWB. We find that 5-10% of the variance in responses to single-question survey measures of SWB is accounted for by the additive effects of the SNPs measured on presently-used genotyping platforms. A correction for measurement error in the SWB measures raises the point estimates to the range 12-18%.

We interpret our findings as indicating that the common narrow heritability is smaller than the typical estimates of narrow heritability from twin-family studies (although one recent, large-scale twin-family study estimated narrow heritability in the 10-20% range, as small as our estimates of narrow heritability; see Bartels and Boomsma (2009)). A caveat to this conclusion is that the twin-based heritability point estimates in our Swedish sample are actually lower than the GREML estimates. That raises the alternative possibility that our low GREML estimates are due to anomalously low "true" heritabilities in the data we happened to study, perhaps because the SWB measures that were available in our data tap into recently-experienced SWB to a greater extent than do multi-item dispositional measures of SWB.

There are three reasons why we believe that our interpretation is more compelling than this alternative. First, the twin-based estimates that we report, which are only available from the Swedish sample, are sufficiently imprecise that we have little confidence in the point estimates. Moreover, with a retest reliability of approximately 0.5 in the SWB measure, the measurement-error-adjusted 95% confidence intervals would overlap comfortably

with the consensus estimates from the literature on twin-family studies. Second, we have relatively more confidence in our GREML estimates, which are similar across our Swedish and Dutch samples. Third and relatedly, our interpretation of the data also fits with the evidence regarding personality, another complex behavioral trait for which epistatic interactions have been hypothesized to be important (Lykken, 1982). Twin-based analyses tend to produce heritability estimates for personality around 30-50% (Jang, Livesley, & Vemon, 1996; Johnson, Vernon, & Feiler, 2008), but a recent study finds evidence that a substantial share of the heritability of Neuroticism, Openness, and Agreeableness is due to non-additive factors (Hahn et al., 2012). Two studies applying GREML to personality traits have been published to date, with results remarkably close to those reported here. One study reports estimates of 9 and 12% for neuroticism and extraversion (Vinkhuyzen et al., 2012), respectively, and another reports estimates in the range 4-10% for traits assessed by the Cloninger personality inventory (Verweij et al., 2012).

For SWB, the gap between the common narrow heritability we estimate and the larger estimates of narrow heritability from twin-family studies may imply that some of the narrow heritability is due to rare polymorphisms. For most traits, it is not well understood to what extent rare polymorphisms with substantial effects account for the heritable variation (Gibson, 2012). Until very recently, rare polymorphisms were not measured on standard genotyping platforms, and therefore most hypotheses regarding their role are based on indirect inferences such as that we make here (Visscher, Goddard, Derks, & Wray, 2012b).

Common narrow heritability is the quantity of most direct interest for assessing the potential contributions of genetic data to SWB research. Nonetheless, it may also be of interest to calibrate what our GREML results imply about narrow heritability, given that our GREML estimates do not rely on the same assumptions as the twin- and family-based estimates of narrow heritability. Two well-measured and widely-studied complex traits for which reasonably reliable heritability estimates are available are height and cognitive ability. The twin-based estimates tend to fall in the range 50-80% for adult intelligence (Bouchard & McGue, 2003) and 80-90% for height (Silventoinen et al, 2003b). These estimates provide an upper bound on the narrow heritabilities. Other family-member comparisons—of full biological siblings, half-siblings and parents and their children—suggest that the narrow heritabilities are unlikely to fall below 50% for adult intelligence (Bouchard & McGue, 1981) and 60% for height (Silventoinen, 2003a). By comparison, the one published GREML estimate for height is 45% (Yang et al., 2010), and GREML estimates for cognitive ability have also been around 45% (Davies et al., 2011; Chabris et al., 2012). This evidence suggests that the common narrow heritability that we estimate should be adjusted upward by a factor of roughly 1.5 to recover a ballpark estimate of narrow heritability.

While our empirical contribution in this paper focuses on estimating the common narrow heritability of SWB, we also believe it is important to highlight for SWB researchers that the conclusions that can be drawn from heritability estimates are more limited than is generally understood (for a related discussion, see Bang (2010). Two misconceptions in particular appear to be widespread. First, some scholars erroneously conclude that higher heritability implies less variation left over to be explained by environmental factors. As the authors of the *World Happiness Report* (Helliwell, Layard, & Sachs, 2012) put it, twin studies are often misleadingly understood as "estimating the extent to which happiness depends on genetically based personality differences rather than differing circumstances." However, as Jencks (1980) explained, heritability comprises any genetic variation that *ultimately* contributes to phenotypic variation, regardless of the pathway, and many plausible pathways are in fact mediated by environmental factors. In the terminology of econometrics, the population regression of SWB on all genes—for which heritability is the R^2—is a *reduced-form* regression, but the structural equations describing the true relationship between a gene and SWB may involve many intervening environmental variables. While *some* genes may affect SWB via relatively direct physical pathways—for example, by affecting baseline serotonin levels or dopamine-receptor density—it also seems likely that many genes matter for SWB through their effects on preferences, personality, and abilities, which in turn influence individuals' choices about friendships, marriage, fertility, and occupational choice. Consequently, some of the variance in SWB explained by genes is the same variance that is explained by these environmental factors. Because genetic effects may operate indirectly through environmental variables, the heritability of SWB does not put any bound on the proportion of variance that could be explained by the full set of relevant environmental variables.

Second, findings of higher heritability are sometimes misinterpreted as demonstrating that there is less scope for interventions to increase SWB. For example, in their seminal paper, Lykken and Tellegen (1996) conclude that "trying to be happier [may be] as futile as trying to be taller." Such a claim may or may not be true, but it is in no way implied by the finding that SWB is heritable. The conclusion is incorrect for two distinct reasons. Related to the point above, some genetic effects may be mediated by *modifiable* environmental variables. The very same genotype may cause a person to grow to five feet or six feet tall, depending on nutritional intake. Furthermore, as Goldberger (1979) pointed out, even if heritability were 100% and the genetic effects operated entirely through mechanisms that are difficult to modify, there may still exist powerful environmental interventions that do not contribute to outcome variance in the current population. As Bang (2010) emphasized in her discussion of genetics and SWB, a heritability estimate represents the fraction of variance explained by genes in a specific population at a specific point in time. Using econometric terminology, one set of explanatory variables (in this case, genes) having a

high R^2 does not rule out a large coefficient on another variable (an intervention), if the latter explanatory variable varies little across individuals in the population under study. In Goldberger's example, the introduction of eyeglasses dramatically improves vision even though eyesight is highly heritable.

To summarize what *can* be concluded from our findings, the magnitude of common narrow heritability provides useful information regarding the potential contributions of genetic data for research on SWB. Because our estimates are lower than typical heritability estimates for SWB, our results suggest that the scope for uses of genetic data that rely on substantial predictive power—such as using a set of polymorphisms as control variables, instrumental variables, or moderators in social-science research—may be more limited than has been assumed. At the same time, the fact that our estimates of common narrow heritability are non-negligible suggests that—even if much of the broad heritability is due to epistatic interactions—some of the SNPs measured on existing platforms have main effects on SWB. Therefore, gene-discovery efforts with a large enough sample size are likely to be successful.

CHAPTER 6

A GWAS on Serial Self-employment

Based on Koellinger et al. (2013).

Abstract

Entrepreneurship has been shown to be partially heritable. Yet, attempts to identify specific genetic polymorphisms underlying the heritable variation of entrepreneurship have until now been unsuccessful, possibly because the available sample sizes for genetic discovery were too small and the available proxy for entrepreneurship (i.e., self-employment) was too broad. In this paper, we present results of a genome-wide association study on serial self-employment. Our study investigated 5,930 individuals from two Dutch samples and tested over two million genetic markers for association with this more narrow measure of entrepreneurship. We attempted to replicate the discovery results in a third, Swedish sample of 2,771 individuals. Our study identifies a novel genetic polymorphism that replicates in the Swedish sample (rs3774790 in the ABHD5 gene). However, a very cautious interpretation of this finding is warranted for several reasons, including a failed attempt to replicate the association with being self-employment at least once in an independent sample of 33,138 Europeans. Furthermore, none of the previously suggested candidate genes is significantly associated with serial self-employment or any other proxy for entrepreneurship that we tested. We conclude that no credible genetic associations with entrepreneurship have been discovered yet, including the results of our own study.

6.1 Introduction

A large and growing body of research is focused on estimating how much of the behavioral trait variation across individuals can be statistically accounted for by genetic factors, including several studies that investigate entrepreneurial behavior (Nicoalou, Shane, Cherkas, Hunkin, & Spector, 2008a; Nicolaou, Shane, Cherkas, & Spector, 2008b, 2009; Nicolaou & Shane, 2009, 2010; Zhang et al., 2009, Shane, Nicolaou, Cherkas, & Spector, 2010; Van der Loos et al., 2013b). Most of these analyses are twin studies, which estimate the heritability of a trait by comparing the correlation of the trait in monozygotic (MZ) twin pairs to the correlation in dizygotic (DZ) twin pairs. Such studies suggest that entrepreneurship and a wide range of other important economic behaviors and outcomes—including income and education (Bowles & Gintis, 2002; Taubman, 1976), investing behavior (Cesarini, Johannesson, Lichtenstein, Sandewall, & Wallace, 2010), overconfidence (Cesarini, Lichtenstein, Johannesson, & Wallace, 2009b; Cesarini, Johannesson, Magnusson, & Wallace, 2012), risk taking (Cesarini, Dawes, Johannesson, Lichtenstein, & Wallace, 2009a), and leadership (Chaturvedi, Zyphur, Arvey, Avolio, & Larsson., 2012)—are moderately heritable. Although twin and family studies can establish that genetic factors account for some of the variation in a trait, they do not identify specific genes or the biological pathways through which genes function.

Information about the genetic pathways to economic behaviors and outcomes could be valuable for several reasons (Benjamin et al., 2012a). First, such knowledge has the potential to improve our understanding of the causes of individual differences, such as risk taking and optimism. Second, suppose a set of genetic polymorphisms taken jointly were found to capture a non-neglible share of variance of a behavioral trait. Then an index constructed from these polymorphisms could be used in (otherwise non-genetic) empirical work as a control variable or as a measure of otherwise-unobserved traits of interest. For example, empirical studies that attempt to identify factors that make some managers more successful than others may benefit from controlling for the entrepreneurial tendencies of managers, which may be inferred to some extent from genetic data. Management scholars have also argued that the prediction of entrepreneurial propensity using genetic data could have practical applications in business and for individual decision making (Nicolaou et al., 2008a; Nicolaou & Shane, 2010; Shane 2010)—however, some such uses of the data (e.g., to screen job applicants) raise ethical issues, and appropriate regulations will be needed to prevent discriminatory practices. Third, incorporating genetic insights into social science may lead to a better understanding about how specific environmental conditions influence behavior and outcomes, for example by attenuating or accentuating the entrepreneurial propensity of individuals.

Whether these theoretical possibilities are practically attainable hinges on the identification of genetic polymorphisms that are robustly associated with entrepreneurship. At the

minimum, it would be required that a non-trivial share of the variance in entrepreneurial propensity across individuals could be attributed to a set of genetic polymorphisms considered jointly.

Almost all of the work to date in the social sciences aimed at finding molecular genetic markers uses the so-called "candidate gene approach" (for reviews, see Benjamin et al., 2012a, 2012b and Ebstein, Isarel, Chew, Zhong, & Knafo, 2010). The candidate gene approach consists of testing a set of genetic polymorphisms for association with the outcome of interest, where the polymorphisms are selected on the basis of what is known or believed about their biological function. Most candidate gene studies are based on samples of several hundred participants and apply a statistical significance threshold of $p < 0.05$. In principle, this approach of formulating and testing ex ante hypotheses is reasonable. In practice, however, the findings from candidate gene studies of complex traits have inconsistent replication records (Ioannidis, 2005), especially in the social sciences (Beauchamp et al., 2011; Benjamin et al., 2012a, 2012b; Chabris et al. 2012). Indeed, the editor of the leading field journal *Behavior Genetics* issued an editorial policy on candidate gene studies of behavioral traits that began "The literature on candidate gene associations is full of reports that have not stood up to rigorous replication" and went on to say "…it now seems likely that many of the published findings of the last decade are wrong or misleading and have not contributed to real advances in knowledge" (Hewitt, 2012). The new editorial policy imposes especially strict quality criteria that candidate gene studies must meet to be considered for publication. Most importantly, the journal requires statistically well-powered tests and a direct replication analysis of novel association results in which the same predictor(s), outcome variable, and statistical model are tested in an independent sample (Hewitt, 2012). Other leading journals such as *Psychological Science* and *Nature Genetics* have adopted the same or even stricter guidelines. Going forward, such guidelines may reduce the likelihood of false positive findings (Fowler and Dawes, 2013).

Existing work on the genetics of entrepreneurship illustrates the need for statistically well-powered tests and replication. Nicolaou et al. (2011) report an association between variation in the DRD3 gene and entrepreneurial behavior in a sample of 1,335 female twins. A particular genetic polymorphism was reported to be associated with an 80% increase in the odds of being an entrepreneur. Van der Loos et al. (2011) fail to replicate this association in a sample seven times larger.

Several factors seem to account for the replication problems of candidate gene studies in social science (Beauchamp et al., 2011; Benjamin et al., 2012a). First, many candidate gene studies cannot effectively control for a confound known as "population stratification" (i.e., the problem that genetic variation is often correlated with environmental confound-

ers).[2] If the relationship between the confounder and the genetic variant is responsible for the association in the original sample and is absent in the replication sample, the association will not replicate. Second, the typical dataset in genetic association work has many behavioral measures and many genetic markers. Hence, false positives arise due to multiple hypothesis testing (Shaffer, 1995) because the *p*-values are often not adjusted to reflect the model selection and pretesting. In principle, having an ex ante theory to guide the research should reduce the number of hypotheses being tested. Unfortunately, much of the analytical rigour that a theory-guided approach typically provides is illusory in the context of behavioral genetics because it is difficult to reduce the number of plausible hypotheses purely on theoretical grounds. Indeed, 70% of all genes (thus ≈ 14,000) are expressed in the brain (Ramsköld et al., 2009), and for many of these, a seemingly plausible biological link to behavior—including entrepreneurship—could be hypothesized.

Replication failures of candidate gene studies are not only frequent in the social sciences but also in the study of complex traits in the medical sciences (Hirschhorn, Lohmueller, Byrne, & Hirschhorn, 2002; Ioannidis, 2005). As a result, candidate gene studies have been largely replaced by genome-wide association studies (GWASs) in medical genetics research. In a GWAS, hundreds of thousands of single nucleotide polymorphisms ("SNPs") spread across the genome are individually tested for association with the outcome of interest without any prior hypothesis, usually in very large samples. GWASs have led to many scientific and biological discoveries in medical research that consistently replicate in independent samples (Visscher, Brown, McCarthy, & Yang, 2012a). This recent development has been made possible by the dramatic decline in the cost of genotyping.

Advocates of GWA studies argue that this approach addresses several of the methodological problems of the candidate gene approach. First, it is possible and standard practice in a GWAS to use a large number of genetic polymorphisms to identify population structure using principal component analysis (Price et al., 2006). In contrast to self-reported ethical background, controlling for the principal components of the genetic data has been shown to effectively address concerns about population stratification (Rietveld et al., 2014a). Second, the hypothesis-free study design of GWAS makes the need to correct for multiple testing transparent. As a result, stringent *p*-value thresholds have emerged as the convention for GWASs in the medical literature (McCarthy et al., 2008). Furthermore, the

[2] The problem of population stratification in genetic association studies can be illustrated in a thought experiment by Lander and Schork (1994): Consider a genetic discovery study on chopstick use among a population of individuals of European and Asian descent. Any genetic variant that differs in frequency between the two groups will be associated with chopstick use. However, these associations are of course not causal. Stratification can also be a problem in ethnically homogenous samples because the frequency of genetic variants can vary across subgroups. For example, some genetic variants co-vary predictably across geographic regions in the Netherlands (Abdellaoui et al., 2013), and these geographic regions also vary in terms of culture, religion, and socio-economic status of their inhabitants. Not controlling for these patterns could introduce environmental confounds into genetic associations with behavior.

large number of published GWASs from large samples (Hindorff et al., 2013) have convincingly shown that most traits are influenced by a large number of genes (i.e., they are "genetically complex") and that SNPs with an R^2 greater than 0.3% are very rare (Benjamin et al., 2012a). These data have helped researchers to adjust their priors about the plausible effect sizes of genetic polymorphisms. Because of these insights, medical researchers have increasingly recognized the importance of very large datasets that have sufficient power to detect even very small genetic effects at conservative *p*-values. The fact that GWAS studies tend to have larger samples is a third advantage. The GWAS approach has enabled an unprecedented surge in genetic discoveries that replicate consistently (Hindorff et al., 2013; Visscher et al., 2012a), including the recent discovery of genetic associations with the biological distal, behavioral trait of educational attainment (Rietveld et al., 2013c). Obviously, the data-driven GWAS approach requires much larger data sets to be successful due to the huge (albeit transparent) multiple testing problem, which requires much stricter *p*-value thresholds.

Our present study is most closely related to Van der Loos et al. (2013b), who conducted a large-scale GWAS on self-employment in a sample of 53,898 individuals from Europe and the US. Their analysis did not find any genome-wide significant results, although they were well-powered to detect common genetic markers with an odds-ratio of 1.11 or higher.[3] Furthermore, Van der Loos et al. (2013b) also found no evidence that any of the genes that were previously suggested in the literature to influence entrepreneurship (Shane, 2010) reveal significant associations with self-employment, although virtually all twin studies on the heritability of entrepreneurship also used self-employment as a proxy (e.g. Nicolaou et al., 2008a, 2008b; Zhang et al., 2009). However, Van der Loos' (2013b) study did provide novel evidence that all common genetic variants considered jointly can account for ~25% of the variance in the tendency to become self-employed. Considered in its entirety, the evidence in Van der Loos et al. (2013b) suggests that entrepreneurship is indeed partially heritable, with hundreds or even thousands of common genetic markers with very small effects contributing towards the observed heritability. This suggests that, in principle, common genetic markers that are associated with entrepreneurship *can* be discovered, but that even a sample of more than 50,000 individuals is not sufficiently large to detect the small effect sizes of individual genetic markers on self-employment.

[3] One of the cohorts who participated in the study of van der Loos et al. (2013b), the TwinsUK Adult Twin Registry, also published the results of a GWAS on entrepreneurship separately (Quaye, Nicolaou, Shane , & Mangino, 2012). In this study, entrepreneurship was operationalized as a composite of four measures (business creation, owner-operator of a new business, self-employment, starting a business), counting individuals as entrepreneurs if any of the four questions had been answered affirmatively. Quaye et al. 2012 also did not find genetic association results that pass standard corrections for multiple testing, supporting the conclusion of Van der Loos et al. (2013b) that the true effect size of single genetic markers on entrepreneurship must be very small.

One possible reason for the null-result of the GWAS in Van der Loos et al. (2013b) is that the observable effect sizes could have been attenuated by measurement error and the heterogeneity within the group of self-employed individuals. For example, some people may choose self-employment because they have no viable alternatives for employment, whereas others may choose self-employment to pursue profitable business opportunities, as pointed out by Van der Loos et al. (2013b). In addition, it is imaginable that genes could have different or even opposite effects in different environments. If so, a meta-analysis like Van der Loos et al. (2013b) that pools GWAS results from various environments may end up with average estimated effects for each SNP that are too small to pass the criterion of genome-wide significance. Therefore, a frequently proposed solution to null-results in GWA studies is to gather better measures of the phenotypes in more environmentally homogenous samples (see Rietveld et al., 2013c for a discussion).

In this study, we pursue this strategy in the context of the "quest for entrepreneurial genes" (Van der Loos et al., 2011). More specifically, we study serial self-employment, which is an empirical measure for entrepreneurship that may comprise a more homogenous group of cases than self-employment. An individual is said to be serially self-employed if she has experienced at least two episodes of self-employment. Previous literature found that serial self-employment captures the innovative, growth-oriented dimension of entrepreneurship better than a variable for having been self-employed at least once (Hyytinen & Ilmakunnas 2007; Westhead, Ucbasaran, Wright, & Binks, 2005). Furthermore, scholars have argued that serial entrepreneurs display a unique mindset (McGrath & MacMillan, 2000). They are more likely to enjoy the excitement of starting a business from scratch, realizing an idea and taking it to the market, and they are more likely to run innovative businesses than people who are self-employed only once (Hyytinen & Ilmakunnas 2007; Westhead et al., 2005). Serial self-employment is the only currently available alternative to self-employment as a proxy for entrepreneurship that is available in reasonably large samples with genetic data.

Futhermore, two of the available samples that have these data are large population cohorts from the southern part of the Netherlands that both focus on geographically small regions (the Ommoord neighborhood in the city of Rotterdam and a small town called Rucphen) with highly homogeneous participant profiles and very limited migration in the past decades. Thus, these two samples, with a combined sample size of 5,930, have much less of the environmental heterogeneity that may have contributed to the null results in Van der Loos et al. (2013b). In addition, a third sample from Sweden with 2,771 individuals that also had the required data became available after the discovery analyses were finished and contributed as a replication sample to our study.

To the best of our knowledge, these three are the only currently available samples in which both comprehensive genetic data and a measure of serial self-employment are avail-

able. In addition to our main estimation results, we also conduct and report here several robustness checks and replication attempts using different operationalizations of entrepreneurship that were feasible with existing data.

To summarize, the current chapter reports novel GWAS results on more narrowly defined proxies of entrepreneurship than Van der Loos et al. (2013b). Furthermore, our two discovery samples come from very similar, narrowly defined geographic environments. Thus, we probe to which extent the null result reported by Van der Loos et al. (2013b) may be due to an inappropriately broad proxy for entrepreneurship or environment-specific genetic effects that are masked by meta-analysing GWAS results from diverse environments.

In the next section we describe our data and briefly explain the GWAS method and our estimated model. Thereafter, we present GWAS results as well as gene-based tests that allow us to relate our findings to the candidate gene literature on entrepreneurship (Shane, 2010, Wernerfelt, Rand, Dreber, Montgomery, & Malhotra, 2012). Subsequently, we report robustness checks and additional replication attempts. Finally, we discuss our results and conclude with implications for future research and practice.

6.2 Data

Because of the large number of hypotheses tested in a GWAS, conservative *p*-value thresholds must be applied. To attain adequate statistical power given plausible effect sizes for behavioral traits (Benjamin et al., 2012a), sample sizes larger than those presently available in any individual dataset are required (Koellinger et al., 2010). To obtain a sufficiently large sample to study entrepreneurship, it is therefore necessary to pool results from several samples. Three cohorts from the Gentrepreneur Consortium (Van der Loos, 2010, 2013b) that have detailed data on serial self-employment contributed to this study: The Rotterdam Study (RS, see Hofman et al., 2009), the Erasmus Rucphen Family Study (ERF, see Henneman et al., 2008), and the Swedish Twin Registry (STR, see Lichtenstein et al., 2006). We use the first two studies as our "discovery cohorts", meaning that they were used for the initial analysis. Both discovery cohorts are population samples from narrowly defined regions in the Netherlands. The Swedish Twin sample, which was genotyped after the results of the discovery cohorts became available, comprises our "replication sample", meaning that it was used to try to replicate the initial findings.

Each study used a different type of genotyping array, but in every case the directly-genotyped SNPs have been imputed to the HapMap2 CEU panel to allow comparison and pooling (Marchini, Howie, Myers, McVean, & Donnelly, 2007). After imputation, each sample contains over two million SNPs. Our study uses these imputed data.

We refer to an observation that fits the definition of serial self-employment (i.e., more than one spell of self-employment) as a "case". We compare the cases to "controls", de-

fined as individuals without any recorded self-employment spells. Individuals with only one known spell of self-employment are excluded from the analysis. Leaving individuals that were self-employed only once in the control group would make it difficult to interpret the results because the estimated coefficients would not only reflect the difference between being serially self-employed and not being self-employed but would also reflect the difference between being serially self-employed and being self-employed only once.

While this proxy for entrepreneurship has been shown to capture innovative, growth-oriented individuals better than a variable for having ever been self-employed (Hyytinen & Ilmakunnas 2007; Westhead et al., 2005), it excludes particularly successful entrepreneurs that have worked in the same, self-started company for their entire professional life. One of our samples, RS, allows us to identify individuals who have been self-employed during their entire work life, thus capturing these particularly successful entrepreneurs. As we report below, we conduct robustness checks using this alternative measure of entrepreneurship in RS.

Furthermore, our main definition of serial self-employment excludes individuals from the analysis who were self-employed only once, which may attenuate our statistical power to identify robust associations. To address this potential shortcoming, we also conduct (and report below) robustness checks using a linear regression model for a semi-continuous proxy for entrepreneurship that compares individuals who were never self-employed (coded 0), those that were self-employed only once (coded 1), and those that were self-employed more than once (coded 2).

6.3 Method

6.3.1 Genome-Wide Association Study (GWAS)

We distributed an analysis plan to the discovery cohorts in the spring of 2010. The analysts conducted the analyses locally and uploaded the results to a secure server, following the prespecified protocol. We then meta-analysed the results and approached the replication cohort in spring 2011, who followed the same analysis plan. Before describing our model specification we outline the major challenges that any GWAS should confront.

The very large number of statistical tests that are carried out in a GWAS leads to a severe multiple-hypothesis-testing problem. In our sample, there are over 2 million imputed SNPs. Because SNPs are locally correlated (in so-called “linkage disequilibrium”), testing each individual variant for association with some outcome has been shown to be approximately equivalent to testing one million independent hypotheses (Hoggart, Clark, De Iorio, Whittaker, & Balding, 2008; McCarthy et al., 2008; The International HapMap Consortium, 2005). Stringent significance levels are used in GWASs to maintain the false positive rate at an acceptably low level. A Bonferroni correction for 1 million independent tests suggests that a significance level of 5×10^{-8} is necessary to obtain a family-wide signifi-

cance level of 5%. This level is often referred to as "genome-wide significance" (McCarthy et al., 2008). We use this significance threshold in the present study. In addition, and in line with standard practice in medical genetics, SNPs with a *p*-value of $10^{-5} > p > 5\times10^{-8}$ are categorized as suggestive hits that enter the replication stage along with the genome-wide hits. In the replication stage, it is customary to apply a Bonferroni correction based on the number of independent hits that were tested for replication. For example, if 10 independent suggestive hits enter the replication stage, the corrected significance for a family-wide significance level of 5% would be $p = 0.005$. However, for SNPs that reached genome-wide significance in the discovery stage, a nominal significance at the 5% level is typically considered to be sufficient for reporting a positive replication, under the condition that the overall *p*-value of the meta-analysis improves when the replication cohort is included.

The standard approach in GWAS for dealing with the problem of population stratification is threefold. First, restrict attention to individuals with a relatively homogenous ethnic background (McCarthy et al., 2008). In our study, all three cohorts consist almost entirely of white European Caucasians. The two discovery cohorts have a particularly homogenous sample of individuals. One of them (ERF) consists entirely of decents of a few original founders of Rucphen. Individuals whose genetic data revealed that they had a different genetic ancestry than the majority of the sample were removed from the analyses in all datasets.

Second, control for any remaining population substructure by including principal components (PCs) of the genome-wide data as controls in the regressions of the phenotype on the individual SNPs (Price et al., 2006). Our analysis plan followed the standard practice in medical genetics and instructed cohorts to control for the first four PCs. In European cohorts, it has been demonstrated repeatedly that the first two or three PCs capture a geographic component of ancestry that is often correlated with different religion, culture, and socio-economic status (Abdellaoui et al., 2013). These first two or three PCs typically control effectively for population stratification, whereas adding more than four PCs does not tend to change the results (Price et al., 2006, Rietveld et al., 2014a). The RS and STR cohorts followed this procedure. In the ERF data, controlling for PCs is not appropriate because the sample consists essentially of only one large family and population stratification is therefore not an issue.

Third, apply "genomic control" (Devlin & Roeder, 1999) to the results to correct for remaining population stratification in the cohorts. This is a simple adjustment based on the assumption that population stratification increases the variance of the estimated test statistics by a constant, which increases the number of expected false positive results. Genomic control involves computing a variance inflation factor, called λ, using the median test statistic. The variance inflation factor λ has a minimum value of 1 and increases in the pres-

ence of population stratification. The factor also increases if the trait being studied is highly polygenic and the effects of all SNPs have been estimated very precisely (Yang et al., 2011). Genomic control (GC) refers to the procedure of mechanically dividing all estimated test statistics by the constant λ. This procedure effectively controls for population stratification in a wide range of cases, but it tends to be over-conservative for highly polygenic traits. Our analysis plan specified that genomic control will be used at the meta-analysis stage, for each cohort separately (i.e., single GC) and, if necessary, for the meta-analyzed results as well (i.e., double GC). A correction factor of $\lambda \leq 1$ is typically interpreted as evidence against population stratification in the sample, and the estimated *p*-values of the coefficients are not adjusted in this case. Otherwise, the *p*-values are linearly adjusted upward (Devlin & Roeder, 1999).

To avoid spurious findings it is standard in molecular genetics research to apply strict quality controls to the genotypic data. We strictly adhered to these conventions here, following the procedures of the prespecified analysis plan. Markers that did not meet the standard criteria for measurement accuracy were excluded. We also omitted SNPs that did not satisfy at least one of the following criteria. First, imputed SNPs had to be known to have reasonable accuracy ($R^2 \geq 0.40$) because low imputation quality inflates statistical Type I and Type II errors. Second, the SNP had to have a minor allele frequency above 1%. The reason is that genotyping errors are more common in SNPs with lower minor allele frequencies. Finally, to maximize the statistical power of the meta-analysis, the SNP had to be available in both RS and ERF after imputation.

6.3.2 Model specification and meta-analysis

In a GWAS, the trait of interest is tested for association with one genetic marker at a time. The two discovery cohorts ran logistic regressions of serial self-employment on each individual SNP available in the imputed data after quality control. The estimated model is as follows:

$$P(y_i = 1) = \exp(\beta' x_i)/(1 + \exp(\beta' x_i)), \quad (1)$$

where y_i is a dummy for serial self-employment for individual i, x_i is a vector of regressors, and β is the vector of coefficients. The primary regressor of interest, $x_{i,1}$, is the number of minor alleles at this particular locus. If the genotype was not imputed, then this value is always an integer equal to 0, 1, or 2. If the genotype was imputed at this locus, then the variable is equal to the imputed (expected) number of minor alleles. We also control for a set of age dummies ($x_{i,2,..,5}$ = age in four categories) and four principal components of the genotypic data in RS-I and STR ($x_{i,6,..,9}$). In estimated this model separately among women and men, as well as in a pooled analysis that also controlled for sex ($x_{i,10}$).

We performed meta-analysis of the cohort-specific results using METAL software (Willer, Li, & Abecasis, 2010). The program first selects a reference allele for each marker and calculates a weighted *z*-score characterizing the evidence for association across studies, with weights proportional to the square-root of the sample size of each study. The overall *p*-value of each allele is given by $p = 2\Phi(|-z|)$, where Φ denotes the cumulative distribution function of the standard normal distribution. Extreme negative *z*-scores yield a small *p*-value and indicate an allele associated with lower entrepreneurial propensity, whereas extreme positive *z*-scores yield a small *p*-value and indicate a positive association with entrepreneurial propensity.

6.3.3 Gene-Based Test

Based on GWAS results it is possible to test whole genes for association with entrepreneurship using a gene-based test of association implemented by the VEGAS software (Liu et al., 2010). This gene-based test uses information from all the measured SNPs in a gene and may reject the null hypothesis of no association even if no individual SNP reaches the significance threshold. The software uses the *p*-values of SNPs within genes to produce a gene-based test statistic. For each gene an empirical gene-based *p*-value is calculated using simulation. For further details see Liu et al (2010). VEGAS tests ≈ 18,000 genes for association. We run the program on the meta-analyzed GWAS results from all three cohorts and analyze which genes are significantly associated with entrepreneurship, including the genes that have previously been proposed for association in the literature.

6.4 Results

Table 6.1 provides descriptive statistics for our sample. Overall, 5,930 observations are available in the discovery stage (N = 3,448 for females and N = 2,482 for males). The average age in RS is 68.2 (SD = 8.7) and 47.7 years in ERF (SD = 13.4). In the replication stage, 2,771 additional observations from STR are available (N = 1,660 for females and N = 1,111 for males). The mean age is STR is 60.6 (SD = 4.2). Overall, the cases comprise 5.4% of the sample.

6.4.1 GWAS Results

Table 6.2 displays the top SNPs from the pooled analysis. The listed SNPs in Table 6.2 belong to different loci (i.e., are distant from each other on the genome) and are approximately uncorrelated. For each set of correlated SNPs, we include only the one with the lowest *p*-value in the discovery stage. Six suggestive loci with $10^{-5} > p > 5\times10^{-8}$ entered the replication stage in the pooled analysis. One that is located on the *ABHD5* gene (rs3774790) replicates in STR ($p = 3.56\times10^{-7}$ in the discovery cohorts and $p = 6.56\times10^{-5}$ in

STR), yielding a genome-wide significant combined *p*-value of 1.08×10^{-10}. ABHD5 codes for a protein that is involved in the storage of fats in the body (National Center for Biotechnology Information, 2013), and defects in ABHD5 have been linked to a rare medical condition called Chanarin-Dorfman syndrome (Emre et al., 2010). We conducted novel biological annotation analyses and found no evidence for an involvement of ABHD5 in the central nervous system, cognition, memory or neurotransmitters (i.e., biological pathways that are hypothesized to be involved in decision making and entrepreneurship, see Shane 2010). Instead, the coexpression profile of ABHD5 confirms a likely involvement in fat metabolism and also suggests a role in immune function. None of the results from the gender-stratified GWAS analyses reached genome-wide significance.

Figure 6.1 shows the 95% confindence interval of the effect sizes of rs3774790 across the three cohorts. Due to the statistical winner's curse, the estimates in the discovery cohorts ERF and RS are likely to be biased upwards (Ioannides, 2008): although the estimated regression gives unbiased *unconditional* estimates of the true parameter value, the parameter is expected to be biased away from the null hypothesis *conditional* on meeting a stringent significance threshold in a given sample. This winner's curse is likely to be especially severe when the *p*-value of the statistically significant finding is close to the *p*-value threshold, as it is here. In contrast, the estimated effect size in an independently drawn replication sample is unbiased (because the SNP has not been selected based on features of that sample).

As expected, our top hit has a stronger effect in the discovery cohorts than in the replication cohort. Yet, the odds ratio of 1.681 in the replication sample is still relatively large compared to recent evidence from many large scale GWASs on binary complex traits such as having a college degree (Rietveld et al., 2013c), living longer than 85 years (Deelen et al., 2014), or clinical diagnoses such as type 2 diabetes (Steinthorsdottir et al., 2007), Alzheimer's disease (Lambert et al. 2013), or depression (Shyn et al., 2011), none of which have identified individual SNPs with such large effects.[4] GWA studies on several relevant social scientific variables such as cognitive ability (Davies et al., 2011), personality (De Moor et al., 2010, Terracciano et al., 2010; Verweij et al., 2010) or economic preferences (Benjamin et al., 2012b) did not find replicable results at all, although the available sample sizes for cognitive ability and personality were larger than in the present study.

[4] In principle, it is possible that there exist rare genetic variants, or other currently unmeasured variants not sufficiently correlated with the SNPs on current genotyping platforms, with large effect sizes (Freeman et al., 2006). If this were true, large samples would still be required to detect these effects in the future because power depends on the fraction of variance explained, which must be small if the variants are rare (Lee et al., 2012; Verweij et al., 2012; Wray et al., 2011).

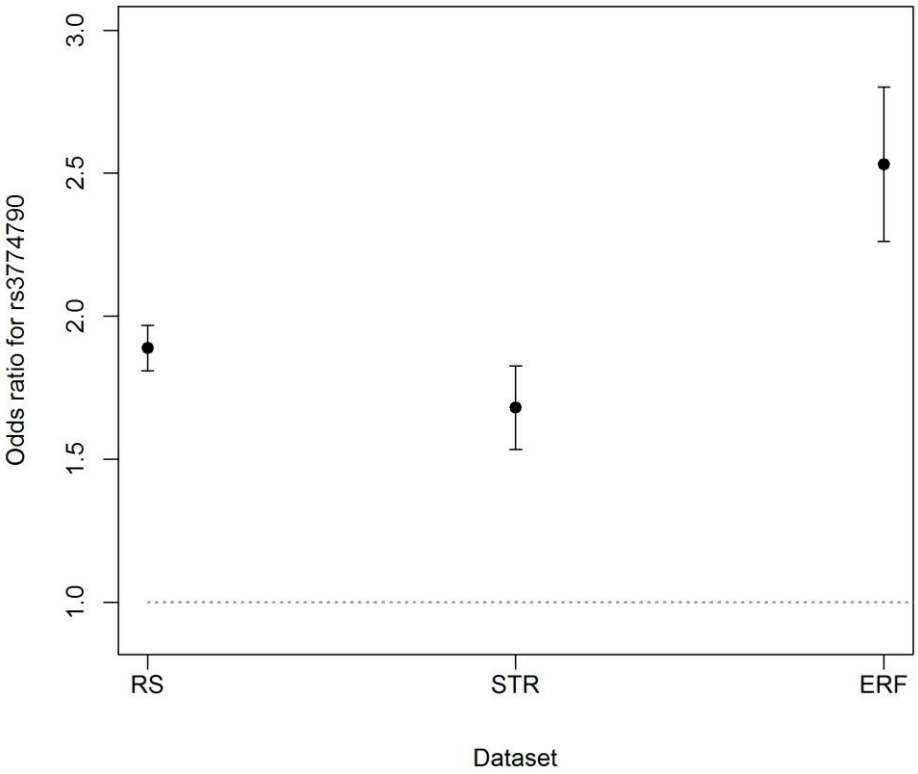
Table 6.1. Sample size of and share of serial self-employment in the studies included in the meta-analysis.

	Males		Females		Pooled	
Study	*N*	Cases	*N*	Cases	*N*	Cases
ERF	400	8.5%	526	6.7%	926	7.5%
RS-I	2,082	4.2%	2,922	2.5%	5,004	3.2%
STR	1,111	16.7%	1,660	3.1%	2,771	8.6%
Total	3,593	8.5%	5,108	3.1%	8,701	5.4%

Table 6.2. Top SNPs resulting from the meta-analysis. SNPs are ordered by *p*-value in the combined meta-analysis, and only the SNP with the lowest *p*-value of each identified locus is listed here. In the column "direction", the studies are in the following order: ERF (λ = 1.108), 2), RS (λ = 1.001), 3), STR (λ = 0.988), where λ is the genomic control parameter.

	Discovery meta-analysis		STR		Combined meta-analysis	
SNP	Average allele frequency	*p*-value	Allele frequency	*p*-value	*p*-value	Direction
rs3774790	0.86	3.56×10^{-7}	0.84	6.56×10^{-5}	1.08×10^{-10}	−−−
rs4748739	0.32	9.33×10^{-6}	0.29	0.11	5.22×10^{-6}	+++
rs17775594	0.88	6.50×10^{-6}	0.89	0.22	9.91×10^{-6}	−−−
rs4479388	0.95	1.75×10^{-6}	0.93	0.51	3.52×10^{-4}	−−+
rs9514109	0.23	6.13×10^{-6}	0.24	0.71	4.26×10^{-4}	−−+
rs4776126	0.28	9.08×10^{-7}	0.28	0.09	2.00×10^{-3}	++−

Figure 6.1. Odds ratios and 95% confidence intervals of rs3774790 across cohorts, ordered by decreasing mean age of cohorts.



6.4.2 Gene-Based Results

We conducted VEGAS gene-based tests for nearly 18,000 using the GWAS results of the discovery stage. This analysis was carried out in the pooled sample, as well as the female and male samples separately. No gene reaches statistical significance at the Bonferroni adjusted significance level of ~2.81×10^{-6}. We additionally tested the 18 candidate genes proposed by Shane (2010) and Wernerfelt et al. (2012) for association with entrepreneurship based on theoretical reasoning and biological function.[5] Furthermore, we investigate the genes that Quaye et al. (2012) highlight as closest to the top 4 loci implicated by their GWA discovery study (although Quaye et al. report in their analysis that none of these loci passed the Bonferroni-correction for multiple hypothesis testing).

[5] The long repeat allele of AVPR1a tested by Wernerfelt et al. (2012) was not directly genotyped in our samples. Wernerfelt et al. (2012) also investigated the MAOA gene, without finding evidence for association with entrepreneurship. The MAOA gene is not available in our GWAS because it is located on the X chromosome, whereas our GWAS only considered autosomal chromosomes.

Table 6.3 reports the results for these theoretical and empirical candidate genes. The Bonferroni-corrected *p*-value for 66 independent tests is 7.58×10^{-4} for a family-wide significance of 5%. None of the candidate genes comes close to this level of significance, including ABHD5, on which the genome-wide significant SNP is located. Under the assumption that the 66 (22×3) tests are independent, under the null hypothesis, we should have expected 6.6 significant associations at the 10% level and 3.3 significant associations at the 5% level. Overall, we observe seven associations in Table 6.3 at a nominal significance level of 10%, and three of these are also significant at a nominal significance level of 5%, close to what one would expect to observe under the null.

Table 6.3. Gene-based *p*-values for 23 candidate entrepreneurship genes based on GWAS meta-analysis of ERF, RS and STR (*N* = 8,701).

Gene	Pooled	Males	Females
Theoretical (Shane, 2010; Wernerfelt et al., 2012)			
ADORA2A	0.732	0.512	0.767
ADRA2A	0.831	0.601	0.074
AVPR1a	0.523	0.996	0.040
COMT	0.084	0.664	0.052
DDC	0.344	0.358	0.795
DRD1	0.841	0.930	0.431
DRD2	0.033	0.414	0.126
DRD3	0.155	0.148	0.177
DRD4	0.737	0.241	0.661
DRD5	0.966	0.624	0.172
DYX1C1	0.676	0.648	0.767
HTR1B	0.805	0.932	0.285
HTR1E	0.311	0.041	0.371
HTR2A	0.758	0.337	0.466
KIAA0319 (DYX2)	0.996	0.521	0.066
ROBO1	0.876	0.603	0.793
SLC6A3 (DAT1)	0.805	0.612	0.798
SNAP25	0.634	0.954	0.598
Empirical (Quaye et al., 2012)			
KIAA1199	0.289	0.720	0.402
OPCML	0.678	0.346	0.860
PARD3B	0.936	0.407	0.998
SYT13	0.542	0.921	0.285

6.4.3 Robustness Checks

We conducted several robustness checks using different proxies for entrepreneurship that were feasible in our data. All quality control filters for the genetic data were identical to our main model specification.

First, we repeated the GWAS analysis in RS by comparing individuals who have been self-employed during their entire work life with those who have never been self-employed. This alternative measure includes particularly successful entrepreneurs who have worked in the same, self-started company for their entire professional life, and excludes individuals who had one or more unsuccessful episodes in self-employment. This alternative specification is only possible in the RS data, which provides the necessary information about the entire work-life history of participants. The sample consists of 138 cases and 4843 controls. No locus reaches genome-wide significance. The odds ratio for rs3774790 is 2.03 ($p = 4.62\times10^{-5}$).

Second, we repeated the GWAS in each cohort and the meta-analyses using a linear regression model for a semi-continuous proxy for entrepreneurship that compares individuals who were never self-employed (coded 0), those that were self-employed only once (coded 1), and those that were self-employed more than once (coded 2). This was possible in all three datasets. The advantage of this model specification is that it includes all individuals who were ever self-employed, which may increase the power of our statistical tests. The disadvantages are that the dependent variable is not continuously distributed and the implicit cardinal interpretation of the data is debatable. Unfortunately, the standard programs for GWAS analysis do not support multinomial logit models or other more appropriate estimation techniques for categorical outcomes. The sample consists of 8,234 individuals without any self-employment record, 1,015 who were self-employed once and 467 who were serially self-employed. SNP rs3774790 has also the lowest *p*-value in the combined meta-analysis of RS, ERF and STR in this model specification. The R^2 of this linear regression specification is 0.28% (SNP coefficient $p = 1.79\times10^{-9}$), and the direction of the SNP's effect is the same as in our main model specification.

Gene-based tests using VEGAS show that none of the candidate genes listed in Table 6.3 is significant after Bonferroni correction in these alternative model specifications, either. Similarily, the gene on which rs3774790 is located (ABHD5) is also not significant in any model specification or sample after the Bonferroni correction for multiple testing has been applied.

Overall, these checks yield results that are qualitatively consistent with our main model specification. Howver, given the unexpectedly large effect size of rs3774790, we scrutinized this result further and found that there are several reasons to remain very cautious about this finding.

The results show that no other locus gets even close to genome-wide significance, whereas rs3774790 and a few neighboring SNPs clearly stick out. That is an odd result for a trait that is most likely highly polygenic (Quaye et al., 2012, Van der Loos et al., 2013b) and does not match the patterns found for other highly polygenic traits (Visscher et al. 2012a) such as educational attainment (Rietveld et al., 2013c) or height (Lango Allen et al., 2010).

Second, rs3774790 is an outlier itself because it is not strongly correlated with most other surrounding SNPs on the same locus. This accounts for the relatively low observed association of the ABHD5 gene with our entrepreneurship proxies in VEGAS tests and makes the interpretation of the finding more difficult because it is unclear if the biological function of rs3774790 can be correctly inferred from biological annotation of ABHD5.

Third, due to the combination of the relatively low minor allele frequency of rs3774790 (≈14%) and the relatively rare event of serial self-employment (≈5%), the effect sizes we estimate are based on a low number of cases for the rare allele (e.g., only 7 individuals who were serially self-employed carried two copies of the minor allele of rs3774790 in the replication sample STR). In principle, this could make the statistical results sensitive to random characteristics of the sample (Roff & Bentzen, 1989). As a robustness check, we ran a logistic regression of rs3774790 on serial self-employment in STR, excluding the 52 homozygotes who have two copies of the rare allele. The estimated odds ratio decreases only marginally from 1.681 to 1.665 ($p = 1.11\times10^{-4}$), suggesting that the results are not driven by this small number of homozygotes. Furthermore, we also conducted Monte Carlo simulations to investigate if the combination of relatively low minor allele frequency and relatively rare outcome could be driving our findings. Although we find evidence for an increased chance for false positives for combinations of very rare MAF and outcomes, the results for our specific scenario show that the estimated *p*-value for rs3774790 in STR is a reasonable approximation for the expected rate of false discoveries.

Fourth and most importantly, rs3774790 is not robust to additional replication attempts we conducted. Specifically, we obtained results from a re-analysis of the data included in the large-scale GWA study by Van der Loos et al. (2013b), excluding the three cohorts that had measures of serial self-employment (ERF, RS, STR) as well as four additional cohorts that did not have genetic information for rs3774790 (HRS, NTR-2, THISEAS, TwinsUK). The analysis is based on the 13 remaining cohorts with a sample size of $N = 33{,}138$, out of which 3,850 cases were self-employed at least once. All of these cohorts were from Western Europe (The Netherlands, Germany, Austria, Italy), Finland, or Iceland and had age profiles that are similar to those in RS, ERF and STR. Under the conservative assumption that rs3774790 only has an effect on serial self-employment and not on being self-employed only once, power calculations strongly suggest that we should be able to repli-

cate the association between rs3774790 and self-employment in these samples. Instead, we found no evidence of association (Odds = 1.03, $p = 0.34$).

6.4.4 Possible Gene×Environment Effects

In principle, it is conceivable that unobserved gene×environment interactions are responsible for our failure to replicate the identified SNP further in additional cohorts because the environmental conditions for entrepreneurship may be different in the replication samples from those in ERF, RS and STR. However, we do not believe that the environments in the replication cohorts were systematically different. Three of the replication cohorts are also samples from the Netherlands (two of which were collected in the same district of Rotterdam as our discovery cohort RS, just a few years later). Three samples are from Germany and one from Austria, countries which are arguably similar to the Netherlands in terms of economic development, institutions and culture. Furthermore, four samples are from Finland and one from Iceland, i.e., environments that may be comparable to that of STR (Sweden). If gene×environment interactions were responsible for the failure to replicate our finding in these additional samples, this would require that the same relevant environmental conditions were present in Sweden, Ommoord and Rucphen, but they were not present in other parts of the Netherlands, Germany, Austria, Finland, and (importantly) also not in samples collected in Ommoord just a few years later. Indeed, the effect of rs3774790 is positive instead of negative in two of the three additional Dutch replication cohorts (NTR—which covers the entire Netherlands—and RS-III—which has been collected in Ommoord) and has Odds ≈ 1 in the third (RS-II, also collected in Ommoord), although we had ≈100% statistical power to replicate the effect at $p = 0.05$ in these three samples. Given that the participants of these cohorts live in environments that are very similar to our discovery cohorts ERF and RS, it is unlikely that unobserved gene×environment interactions are responsible for our failure to replicate rs3774790 further in these cohorts.

It is also difficult to interpret the different effect sizes for rs3774790 in ERF, RS, and STR (see Figure 6.1) as providing much evidence either for or against possible gene × environment interactions. Partly, this is due to considerable estimation error and partly due to the competing hypothesis that the differences between the discovery and the replication cohort are due to the statistical winner's curse (Ioannides, 2008).

In general, however, GWAS meta-analyses may mask the effects of specific genes in specific environments. This is probably a bigger methodological challenge for the study of (serial) self-employment than for traits like body height or eye color that have consistent definitions and interpretations in different countries. One advantage of our study design is that we conduct GWAS discovery in two samples from very similar environments. Nevertheless, we cannot conclusively rule out that more specific environmental conditions than those our study design controlled for may give rise to gene×environment interactions.

6.5 Discussion

6.5.1 Practical Implications

The evidence that entrepreneurship is heritable has prompted scholars to speculate about the use of molecular genetic data for understanding and predicting entrepreneurship (Shane, 2010). It has been suggested that molecular genetic data could allow researchers to tackle interesting new questions such as whether managers and entrepreneurs have similar genetic endowments (Nicolaou & Shane, 2010). It has also been proposed that it may become possible to develop genetic tests that score an individual's propensity to become an entrepreneur (Nicolaou et al., 2008a). However, whether genes could eventually be used to predict outcomes such as entrepreneurship is not only a function of heritability, but also depends on the "molecular genetic architecture" of the trait, i.e., the joint distribution of effect sizes and allele frequencies of the causal genetic variants (Lander, 2011). If a few genes with relatively large effects on entrepreneurship exist, it would be possible to detect them in relatively small samples. If, however, the heritability is accounted for by a large number of genetic variants, each with very small individual effects, identifying these variants and using them for practical purposes would require much larger sample sizes.

Given the sample sizes used in previous work, scholars seeking to identify genes for entrepreneurship were implicitly operating under the assumption that a few genes with large effects exist (Nicolaou et al., 2011; Nicolaou & Shane, 2009; Shane 2010, Wernerfelt et al., 2012). The combined evidence of our study and the results of Van der Loos et al. (2013b) and Quaye et al. (2012) indicate that this assumption is likely to be wrong. Although our pooled sample is 64 times larger than the most recent candidate gene study on entrepreneurship (Wernerfelt et al., 2012), none of the candidate genes that were proposed to have large effects in the previous literature are significantly associated with serial self-employment in our study.

Furthermore, the results of our own genetic discovery did not survive further probes for robustness. Although previous studies provided convergent evidence for the heritability of entrepreneurship (Van der Loos et al., 2013b, Nicolaou et al., 2008a, 2008b; Zhang et al., 2009), studies that investigated the molecular genetic architecture of this trait are most consistent with the hypothesis that entrepreneurship is a genetically complex trait, with many genes exercising small effects each, and possibly depending on environmental factors. We conclude that the existing evidence in its entirety suggests that there are currently no practical uses of molecular genetic data in the context of entrepreneurship.

6.5.2 Directions for Future Research

Given these conclusions regarding the molecular genetic architecture of entrepreneurship, we propose four avenues for future research on the genetics of entrepreneurship. One possibility is to directly examine the possibility for gene×environment interactions. However,

attempts to do so would have to face a number of challenges. First, the large number of possibly relevant environmental conditions increases the multiple testing problem in gene-discovery studies even further. Second, specific environmental conditions make it even more difficult to attempt replication in independent samples. Third, the results of gene×environment studies could be driven by confounders (e.g., ethnicity, gender, age, socioeconomic status) rather than by the specified genetic or environmental variables per se. Keller (2014) concludes that most gene × environment studies have failed to control for such confounders appropriately. A possible intermediate step are study designs that investigate the heritability of entrepreneurship across different environments, or before and after a specific policy intervention.

A second possible avenue for future research is to shift the focus toward variables that may mediate the relationship between genes and entrepreneurship. Examples of such variables that can be measured in large samples may include preferences toward risk and uncertainty, confidence, and optimism. One advantage of this approach is that genetic effects on more proximate outcomes are likely to be stronger and hence easier to detect, for a given sample size, than the genetic effects on distal outcomes, such as entrepreneurship. In addition, it seems likely that the genetic factors that are associated with these proximate outcomes vary less across the different environments that must be pooled when conducting a GWAS meta-analysis. In contrast, genetic markers associated with entrepreneurship may be relatively difficult to detect in part because of differences in the relative importance of the determinants of entrepreneurship differs across environments. A practical limitation of this approach is, however, that the sample sizes to study these more proximate outcomes still needs to be very large (Benjamin et al., 2012b), and accurate measures of economic preferences are rare in genetic datasets. Once such studies become feasible, however, they could generate empirically plausible candidate genes for entrepreneurship.

A third approach is to keep studying self-employment in samples that are even larger than the one Van der Loos et al. (2013b) had available. Although self-employment is a very noisy proxy for entrepreneurship, it will ultimately be available in a much larger sample than any other, better measure for entrepreneurship, because medical cohorts that collect genetic data often ask their participants about employment status as a control variable to study health outcomes. As the available sample sizes for medical research purposes keep increasing, so will the availability of samples with data on self-employment. The recent findings for educational attainment (Rietveld et al., 2013c) provide a proof-of-concept for the potential success of studying a noisy behavioral outcome in a very large sample and outline a statistical framework that illustrates the trade-off between sample size and phenotype quality for GWAS. Indeed, Rietveld et al. (2013c) estimate that they had more power to detect SNPs associated with cognitive performance in their GWAS on educational attainment (N = 126,559) then the largest GWAS that had been conducted on cognitive per-

formance directly (N = 17,989; Benyamin et al., 2014). A recent follow-up study investigated whether the SNPs that were most strongly associated with educational attainment were also associated with cognitive performance in independent samples. This "proxy-phenotype" approach indeed succeeded in identifying novel loci that are robustly associated with cognitive performance (Rietveld et al., 2014b). It is conceivable that a similar proxy-phenotype approach using self-employment data could also help to uncover specific genetic polymorphisms and biological mechanisms involved in entrepreneurship and mediating traits such as sensation seeking (Nicolaou et al., 2008), extraversion and openness to experience (Shane et al., 2010), optimism, or risk preferences.

A fourth route for future research is to use new statistical approaches that make more efficient use of the genetic data in the aggregate to shed light on the biology underlying a trait. For example, Lee et al. (2012) recently found that SNPs involved in the central nervous system explain a disproportionate amount of variance in the liability to schizophrenia. Although their method does not directly identify individual SNPs, it implicates a specific biological systems.

We view these potentially promising directions for future research as complementary, and they can be followed in parallel. However, it is probable that researchers will also continue to conduct traditional candidate gene studies on entrepreneurship. We therefore urge management journals to implement the same quality standards for these types of studies that leading field journals such as *Behavior Genetics* have adopted. Specifically, journals should require statistically well-powered tests, proper adjustment for subtle population stratification in the data, and a direct replication analysis of novel association results in independent samples (Hewitt, 2012).

Finally, once suitable data become available, a further well-powered replication attempt for rs3774790 on serial self-employment, measured in the same way as in our study in another sample from the Netherlands, would be a natural next step.

6.6 Conclusion

The "quest for the entrepreneurial gene" (Van der Loos et al., 2011) is largely motivated by the struggle of scholars to understand entrepreneurs better, what motivates them, and what makes them different from other people. Various research approaches, including tools and theories from economics, psychology, and sociology have been proposed and applied to these questions, yet the answers to "what makes an entrepreneur" remain uncertain and incomplete (Shane & Venkataraman, 2000). Evidence that genes may be part of the answer (Nicolaou et al., 2008a, 2008b, 2009, 2011; Shane and Nicolaou 2013, Zhang et al., 2009) has been received with both great hopes and enthusiasm, as well as with skepticism and critique among scholars and in the media. Here, we contribute to this debate by investigating the genetic architecture of entrepreneurship, measured as serial self-employment, using

three large samples of comprehensively genotyped individuals from the Netherlands and Sweden and state-of-the-art methods from genetic epidemiology.

Our results help to put the insight into perspective that entrepreneurship is partially heritable. Specifically, our empirical evidence is inconsistent with the view that a small number of well-understood genes with strong effects are responsible for the observed heritability of entrepreneurship (Shane, 2010). Instead, we identified a novel locus that showed evidence for association with serial self-employment, but several reasons—including the failure of our replication attempt in another large, independent sample—suggest that one should remain very cautious about this finding, even though our study applied state-of-the-art methods and stringent criteria for data quality.

Thus, considering the findings of Van der Loos et al. (2013b), Quaye et al (2012), and our study jointly, we conclude that the hopes and fears related to possible applications of genetic predictions of entrepreneurial propensity (Nicolaou et al., 2008a, 2008b; Shane, 2010) are currently not warranted yet. The extent to which genetic prediction will become possible in the future depends on two factors. First, prediction accuracy increases with the sample size of comprehensively genotyped individuals that can be used to study an outcome (Goddard, 2009). Yet, recent findings for educational attainment (Rietveld et al., 2013c) suggest that samples of more than 100,000 individuals are likely to be needed to predict even small shares of ~2% of the variance in behavioral outcomes from genetic data alone. In the study by Van der Loos et al. (2013b), a best-fitting linear combination of all SNPs included in their study captured less than 0.2% of the variance in self-employment, derived from a GWAS discovery sample of $N = 50{,}627$. Thus, sample sizes that are much larger than what is currently available will be needed before useful applications of genetic data for empirical research purposes can be developed in the context of entrepreneurship.

Second, the variance explained by a best-fitting linear combination of all SNPs also depends on how stable the influence of specific genes on entrepreneurial propensity is in different environments. Given the currently available evidence, it is too early to conclude that specific genes exist that have a universal influence on entrepreneurship that is independent from environmental conditions.

However, the available empirical evidence also suggests that future research could in principle identify genes that influence entrepreneurial behavior, even though the effect of every single gene that will be discovered is likely to be small. But given the consistent evidence on the heritability of entrepreneurship, the interest of many scholars in this trait, and the fact that rough proxies for entrepreneurship (i.e., self-employment) will become available in ever larger genetic datasets in the future, we expect that research on genetic and biological influences on entrepreneurship will remain an active and potentially rewarding field of research.

CHAPTER 7

Self-employment and Health

Based on Rietveld, Van Kippersluis, & Thurik (2014).

Abstract

The self-employed are often reported to be healthier than wage workers; however, the cause of this health difference is largely unknown. The longitudinal nature of the US Health and Retirement Study allows us to gauge the plausibility of two competing explanations for this difference: a contextual effect of self-employment on health (benefit effect), or a health-related selection of individuals into self-employment (barrier effect). Our main finding is that the selection of comparatively healthier individuals into self-employment accounts for the positive cross-sectional difference. The results rule out a positive contextual effect of self-employment on health, and we present tentative evidence that, if anything, engaging in self-employment is bad for one's health. Given the importance of the self-employed in the economy, these findings contribute to our understanding of the vitality of the labor force.

7.1 Introduction

Many governments stimulate self-employment (Gilbert, Audretsch, & McDougall, 2004; European Commission, 2004) because of the assumed positive link with economic vitality (Audretsch & Keilbach, 2004; Carree & Thurik, 2010; Koellinger & Thurik, 2012). Recently, self-employment was also suggested to have a positive link with individuals' physical vitality (Tetrick, Slack, Da Silve, & Sinclair, 2000; Bradley & Roberts, 2004; Stephan & Roesler, 2010). If such a link exists, governments may also want to encourage self-employment as an alternative to early retirement to relieve the economic pressures generated by ageing populations. The effectiveness of these measures depends on the extent to which self-employment indeed positively affects the health of the 50+ population. Existing evidence on this topic is, however, (i) scarce, (ii) conflicting, and, partly due to the cross-sectional nature of existing analyses, (iii) poorly understood (Torres, 2012). This is surprising given the importance of the self-employed in the current economic system (Audretsch & Thurik, 2000, 2001).

While some of the earlier-mentioned papers show that self-employment has health benefits, others show that the self-employed are at higher risk for certain diseases than wage workers (Buttner, 1992; Jamal, 1997; Lewin-Epstein & Yuchtman-Yaar, 1991; Parslow et al., 2004; Dahl, Nielsen, & Mojtabai, 2010). All cited studies emphasize structural differences between self-employment and wage work to explain the difference in health between the self-employed and wage workers. The self-employed operate their business independently, without the control of a supervisor, while wage workers are not fully responsible for the survival of the business (Bjuggren, Johansson, & Stenkula, 2012). The associated differences in the amount and intensity of work and freedom versus controllability may result in different health outcomes (Stephan & Roesler, 2010).

Another explanation for health differences is almost entirely overlooked; namely, the selection of comparatively healthier individuals into self-employment. Only Jamal (1997) and Stephan & Roesler (2010) mention this possibility in their study limitations as an alternative explanation for their findings.[6] Such a selection mechanism is difficult to reveal because instrumental variables or longitudinal data are required.

In this paper, we use the Health and Retirement Study (HRS, Juster & Suzman, 1995), a population-wide panel dataset with information about employment status and several health outcomes, to study the association between self-employment and health. The longitudinal nature of the HRS allows us to gauge the plausibility of a contextual effect versus a selection effect, which is essential to fully understand the association between self-

[6] Yoon and Bernell (2013) use an instrumental variables approach to overcome the selection problem, yet their instruments include the number of self-employed family members, immigrant status, years of labor market experience, the number of children, and having uninsured children, which are likely to have a direct relation with health, and thus violate the exclusion restriction.

employment and health. Because it remains notoriously difficult – even with longitudinal data – to discriminate between the two effects, we use several methods to investigate which effect prevails.

We show that the self-employed are generally healthier than wage workers for all three available measures of health: number of health conditions ever had, self-reported health and mental health. This correlation does not disappear when controlling for health history, suggesting that contemporaneous reverse causality from health to self-employment cannot entirely explain the correlation. However, the longitudinal fixed-effect analyses rule out a positive contextual effect of self-employment on health. These results suggest that the selection of comparatively healthier individuals into self-employment accounts for the cross-sectional association. We present tentative evidence that the contextual effect of self-employment on health could even be negative if the selection into self-employment based on unobservables is as large as the selection based on observables.

7.2 Related Literature

Health can be influenced by the characteristics of a given occupation (Ravesteijn, Van Kippersluis, & Van Doorslaer, 2013), which may result in a "contextual effect" of self-employment on health. In contrast, self-employment can attract individuals with a different health profile and prospect than wage workers. This could occur when individuals decide to quit or enter self-employment for health reasons, and when pre-determined individual cognitive and non-cognitive skills simultaneously affect health and self-employment decisions. We will denote the latter as the "selection effect", and discuss each of the two effects below.

7.2.1 The Contextual Effect

A useful theoretical framework for understanding the contextual effect of self-employment on health is the so-called job-demand-control model (Karasek, 1979; Karasek & Theorell, 1990; Theorell & Karasek, 1996) that is rooted in sociology and epidemiology. The model emphasizes two aspects of the work environment, job control and job demand, that relate occupational characteristics to health. Job control refers to how much decision-making authority an individual has over when and how to perform the necessary work. Job demand refers to the experienced work intensity and workload. The mismatch between job demands and job control determines the level of occupational stress, which can influence disease incidence and longevity (Cooper & Marshall, 1976; Karasek, 1979; Cooper & Smith, 1985).

Compared to wage workers, the self-employed have higher levels of job control. As owners of their business, the self-employed have more control over the organization of different tasks and the allocation of resources (Hébert & Link 1989; Prottas & Thompson,

2006). These positive features of self-employment also have a downside, which has been called "a double-edged sword" (Lewin-Epstein & Yuchtman-Yaar, 1991). The self-employed experience higher levels of job demands and workload as opposed to wage workers (Buttner, 1992; Stephan & Roesler, 2010). Self-employment can turn into "self-exploitation" as income, job, property, and assets are at stake (Lewin-Epstein & Yuchtman-Yaar, 1991).

An additional mechanism through which self-employment potentially affects health is the lack of health insurance (Zissimopolous & Karoly, 2007). This may have an effect on health if the self-employed through the use of too little or inappropriate medical care, and even directly decrease mental well-being and increase anxiety about financial matters (Finkelstein et al. 2012).

The empirical evidence regarding structurally different influences on health of self-employment and wage work is both limited and mixed, and the relative strengths of the positive (job control) and negative (job demand, lack of health insurance) health stimuli of self-employment have not been assessed.

7.2.2 The Selection Effect

The entrance into self-employment may be associated with an individual's health status for several reasons. First, ill health decreases the ability to focus on business opportunities (Gielnik, Zacher, & Frese, 2012) Second, ill health may limit the access to crucial start-up financing (Klapper, Amit, Guillen, & Quesada, 2007; Beck & Demirguc-Kunt, 2006). Third, self-employment is a financially less attractive option compared to wage-work for less healthy individuals, because income in self-employment hinges much more on the individual ability to work. Fourth, less healthy individuals may stay in wage-work because it would be more expensive or impossible to be insured while self-employed.

The aforementioned arguments all would suggest a positive selection of healthier individuals into self-employment. Nonetheless, those with health problems may also have strong difficulties finding suitable wage work. Employers may discriminate against them in the job-selection procedure, which could push them into so-called necessity self-employment (Verheul, Thurik, Hessels, & Van der Zwan, 2010). The empirical evidence about health as an explanatory variable for self-employment is however mixed and limited. Using the HRS, Zissimopoulos and Karoly (2007) show that having a health limitation is a pull factor into self-employment. However, Fuchs (1982), Evans and Leighton (1989) and Van Praag and Van Ophem (1995) all show that having a health limitation is not associated with the transition from wage work to self-employment.

Self-employment is also associated with sociodemographic characteristics that independently affect health and health behavior (Lewin-Epstein & Yuchtman-Yaar, 1991), such as age (Zissimopoulos & Karoly, 2007; Parker, 2009), education (Blanchflower, 2000;

Lleras-Muney, 2005), perseverance (Beugelsdijk & Noordhaven, 2005), and risk aversion (Ekelund et al., 2005). This implies that there are several reasons to expect that individuals entering self-employment have a different health profile than wage workers. However, in which direction the joint effect of this selection mechanism points remains unclear.

Most existing papers use cross-sectional data from which, in the absence of exclusion restrictions, it is difficult to disentangle the contextual effect of self-employment on health from a selection effect.[7] In our study, we focus on the aggregate 'net' contextual effect and the aggregate 'net' selection effect. The longitudinal nature of our data allows us to study which of these two effects prevails.

7.3 Data

Our study uses the Health and Retirement Study, a longitudinal panel study that surveys a representative sample of Americans over the age of 50 every two years. The dataset has three advantages: first, the HRS is a population-wide study and thus includes both the self-employed and wage workers. Second, the sample of relatively older individuals represents a phase of life in which many health issues become relevant and apparent and in which there is much policy scope to increase labor-force participation rates. Third, the dataset includes information on several health measures. Despite these advantages, the generalizability of our findings to other age-groups may be limited.

We use the HRS RAND v.L dataset, which consists of ten biennial waves of data collection (1992–2010). The HRS RAND v.L dataset includes 30,671 individuals, coming from five subsamples. The initial HRS cohort (N=13,635, born between 1931 and 1941) and AHEAD cohort (N=8,334, born before 1924) participate from wave one onwards. The CODA cohort (N=2,420, born between 1924 and 1930) and WB cohort (N=2,760, born between 1942 and 1947) participate from wave four onwards. The EBB cohort (N=3,522, born between 1948 and 1953) joined in wave seven.

We study three health indicators as dependent variables: number of health conditions, self-reported health and mental health. We dichotomize these measures to ensure compatibility for all of our empirical methods, but made sure that are not driven by this dichotomization (see section 7.5 for robustness checks).

The number of health conditions is measured using a 9-point scale, indicating for a set of 8 common chronic diseases (arthritis; cancer; diabetes; heart problems; high blood pressure; lung disease; psychiatric problems; stroke) how many of these a doctor has *ever* told the respondent that he or she has. Our binary variable *No Health Conditions* takes the val-

[7] An exception is Dolinksy & Caputo (2003), who show in a longitudinal sample of women that self-employment has no effect on health, whereas working for wages has a positive effect on health. The significance of the effect difference is, however, not provided, and selection into self-employment is assumed to occur only on the basis of observables.

ue 1 if a person has none of the mentioned diseases and 0 otherwise. Self-reported health is measured on a 5-point Likert scale, with 1: Excellent, 2: Very good, 3: Good, 4: Fair, and 5: Poor. Our binary variable *Self-reported Health* takes the value 1 if self-reported health is Excellent or Very good and 0 otherwise. Mental health is measured on a 9-point CESD (Center for Epidemiological Studies Depression Scale) scale, ranging from 0 (absence of depression symptoms) to 8 (presence of all measured depression symptoms). CESD is consistently measured in wave 2-10 (wave 1 uses a different scale); therefore, we only use the variables of wave 2-10. Our variable *Mental Health* takes 1 if CESD equals 0 and 0 otherwise.

Our main explanatory variable is the binary variable *Self-employment*. In each wave, those who identified as self-employed or to be running their own business are coded as 1, and those who identified as working for someone else are coded as 0.[8] In addition, we have the following demographic control variables: *Gender* (0: female, 1: male), *Age* (in years at time of interview), *Age-squared*, *Race* (0: white, 1: non-white), *Years of education* (0 – 17+ years), *Years of education father* (0 – 17+ years), and *Years of education mother* (0 – 17+ years). These are well-known factors influencing health and self-employment that are, in general, determined before labor force entrance. The variables *Industry* (1: Primary sector, 2: Secondary sector, 3: Tertiary sector)[9], *Job type* (1: White collar, 2: Blue collar, 3: Other)[10], and *Working hours* (1: 0-10, 2: 11-30, 3: 31-50, 4: 51+) are constructed to control for heterogeneity within *Self-employment*. We refer to these three variables as the employment controls.

All person-year observations with complete information on health, demographics and employment are included in the analysis, except those with an age higher than 65 (the normal retirement age, and the age at which Medicare becomes available). This results in a sample size of 44,930 (12,247 individuals) for *No Health Conditions* and *Self-reported Health*. A subsample of 35,649 (10,723 individuals) observations is available for *Mental Health* because this variable has no observations in wave 1. Descriptive statistics of the sample are presented in Table 7.1. In total, there are 36,461 person-year observations for wage workers and 8,469 for the self-employed. Differences in health between the self-employed and wage workers are small but apparent. Differences in the mean values of the control variables indicate the necessity to control for these observables.

[8] Because our interest is the comparison between the self-employed and wage workers, we do not construct a separate group of retired or unemployed individuals. Our study sample thus reflects the working population.
[9] The primary sector includes agriculture, forestry, fishing, and mining (, & construction). The secondary sector includes manufacturing, utilities, and construction. The tertiary sector includes all other job industries.
[10] We followed Forman-Hoffman et al. (2008) in the construction of this categorical variable.

Table 7.1. Descriptive statistics of the analysis sample. Mean values are reported, and standard deviations are given in parentheses. For the categorical employment controls, percentages are given per category.

	Wage workers	Self-employed
Health measures		
No Health Conditions (0/1)	0.36 (0.48)	0.39 (0.49)
Self-reported Health (0/1)	0.57 (0.49)	0.61 (0.49)
Mental Health (0/1)	0.54 (0.50)	0.56 (0.50)
Demographic controls		
Gender (0: female, 1: male)	0.42 (0.49)	0.57 (0.49)
Age (years)	55.88 (5.15)	56.74 (5.01)
Race (0: white, 1: non-white)	0.18 (0.39)	0.11 (0.32)
Years of education (0-17+ years)	13.21 (2.81)	13.46 (2.80)
Years of education father (0-17+ years)	9.80 (3.94)	10.25 (3.88)
Years of education mother (0-17+ years)	10.12 (3.53)	10.60 (3.52)
Employment controls		
Industry		
Primary sector	4.87%	16.67%
Secondary sector	17.71%	8.76%
Tertiary sector	77.43%	74.57%
Job type		
White collar	65.96%	62.94%
Blue collar	32.77%	30.88%
Other	1.27%	6.19%
Working hours		
0-10	2.72%	8.89%
11-30	14.10%	26.89%
31-50	73.80%	40.71%
51+	9.38%	23.51%
N, person-year observations	36,461	8,469
N, individuals	10,399	3,050

Note: The sum of individuals in wage-work and self-employment is larger than the total sample size of 12,247 individuals due to switchers between wage-work and self-employment.

7.4 Methods and Results

7.4.1 Pooled Regressions Controlling for Observables

First, we compare the average health status of the self-employed with that of wage workers. Using pooled logit regression, we explain *No Health Conditions*, *Self-reported Health* and *Mental Health*. In these models, a significant positive coefficient for *Self-employment* means that the self-employed are healthier than wage workers. Wave dummies are included in each regression, and the standard errors are clustered at the individual level. We run three model specifications for each dependent variable. In the first specification, we only include *Self-employment*, which produces the simple association between self-employment and health. In the second specification, we add the demographic control variables to investigate whether observed characteristics such as education and age are responsible for the

association between self-employment and health. In the third specification, we add the employment controls to verify that the association not simply reflects differences in the industry sector, occupational level, or working hours across the self-employed and wage workers. The results are presented in Table 7.2. The regression coefficients for the demographic controls in the second specification are not reported, because they are very similar to those in the model including both demographic and employment controls.

Table 7.2. Regression coefficients for *Self-employment* in the logit models explaining *No Health Conditions, Self-reported Health* and *Mental Health*.

	No Health Conditions	Self-reported Health	Mental Health
Pooled Logit			
Self-employment	0.15** (0.04)	0.16*** (0.04)	0.10** (0.04)
+ Demographic controls	NO	NO	NO
+ Employment Controls	NO	NO	NO
Pooled Logit			
Self-employment	0.17*** (0.04)	0.10** (0.04)	0.01 (0.04)
+ Demographic controls	YES	YES	YES
+ Employment Controls	NO	NO	NO
Pooled Logit			
Self-employment	0.17*** (0.05)	0.11** (0.04)	0.03 (0.04)
Gender	0.18*** (0.04)	-0.08* (0.04)	0.27*** (0.03)
Age	-0.03 (0.04)	-0.03 (0.03)	-0.01 (0.03)
Age-squared	-0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Race	-0.15** (0.05)	-0.49*** (0.04)	-0.31*** (0.04)
Years of education	0.03** (0.09)	0.13*** (0.01)	0.06*** (0.01)
Years of education father	0.01 (0.01)	0.02** (0.01)	0.02*** (0.01)
Years of education mother	-0.01 (0.01)	0.03*** (0.01)	0.02** (0.01)
Industry (base: Primary sector)			
Secondary sector	0.00 (0.09)	-0.03 (0.07)	-0.02 (0.07)
Tertiary sector	-0.05 (0.08)	-0.05 (0.06)	-0.01 (0.07)
Job type (base: White collar)			
Blue collar	-0.12** (0.04)	-0.27*** (0.04)	-0.28*** (0.04)
Other	0.07 (0.13)	-0.22* (0.11)	-0.32** (0.11)
Working hours (base: 0-10 hours)			
11-30	-0.04 (0.07)	0.05 (0.07)	-0.06 (0.06)
31-50	0.00 (0.07)	0.10 (0.06)	-0.04 (0.06)
51+	0.06 (0.08)	0.18* (0.07)	-0.15* (0.07)
N, person-year observations	44,930	44,930	35,649
N, individuals	12,247	12,247	10,723

Note: Standard errors in parentheses and clustered per individual; $^{*}p < 0.05$. $^{**}p < 0.01$. $^{***}p < 0.001$.

The coefficients for *Self-employment* are all positive and statistically significant in the univariate regressions for *No Health Conditions, Self-reported Health,* and *Mental Health*. Odds ratios are respectively 1.15 for *No Health Conditions*, 1.17 for *Self-reported Health*, and 1.11 for *Mental Health*. The inclusion of demographic and employment controls lowers the value of the coefficient in the *Self-reported Health* regression. The coefficient remains, however, significant. For *Mental Health*, the coefficient also becomes smaller, but becomes insignificant. Interestingly, the adjustment for demographics and employment characteristics increases the *Self-employment* coefficient in the *No Health Conditions* regression. Altogether, we find that the self-employed are in better health than wage workers, although the difference in mental health is not statistically significant once demographic variables are controlled for.

Among the diseases that make up the *No Health Conditions* variable we find that from the 8 underlying diseases, heart problems ($p = 0.008$), and high blood pressure ($p = 0.001$) are significantly negatively associated; the self-employed have these conditions less often than wage workers. The other health conditions, arthritis ($p = 0.06$), cancer ($p = 0.59$), diabetes ($p = 0.13$), lunge disease ($p = 0.14$), psychiatric problems ($p = 0.88$), and stroke ($p = 0.24$) are not significantly associated at the five-percent level.

7.4.2 Regressions Controlling for Lagged Health and Time-Invariant Unobservables

Next, we perform longitudinal analyses to investigate reverse causality from health to self-employment, if health is a pull or push factor into or out of self-employment. Inspired by Granger (1969), Adams, Hurd, McFadden, Merrill, & Ribeiro (2003), and Stowasser, Heiss, McFadden, & Winter (2011), we investigate whether the lagged self-employment status has explanatory power for current health, while controlling for lagged health. A coefficient for self-employment that is qualitatively similar to the coefficient for self-employment in the pooled logit regression would strongly suggest that the association between self-employment and health is not completely the result of reverse causality. Again, we use a pooled logit regression with wave dummies and standard errors clustered per individual. As dependent variables, we take only *Self-reported Health* and *Mental Health*. The way in which *No Health Conditions* is measured in the HRS makes it unsuitable for inclusion in longitudinal analyses.[11] Again, we implement three model specifica-

[11] *No Health Conditions* is measured in such a way that it only increases with age because the question is asked whether the doctor has *ever* told the respondent to have a certain chronic condition. The only possible change is from 0 (no health condition ever had) to 1 (at least one health condition ever had). This approach makes the correlation between measures in two consecutive waves almost 1. Moreover, this measure does not necessarily precisely reflect the change in the health status of an individual. For example, someone completely recovered from a heart attack will always be seen in the data as having at least one health condition.

tions; the only difference is that we include a lag of the dependent variable and the lag of *Self-employment* instead of current *Self-employment*.

Panel 1 of Table 7.3 reports the results of a logit regression with a lagged dependent variable to establish whether the cross-sectional results are the result of reverse causality between self-employment and health. We find qualitatively the same results as those presented in Table 7.2.[12] The coefficient for *Self-employment* is significant in the regressions for *Self-reported Health*. For *Mental Health*, only the univariate model shows this association. We conclude that for these two health measures, the association from Table 7.2 cannot be entirely due to reverse causality.

Table 7.3. Regression coefficients for *Self-employment* in the models explaining *Self-reported Health* and *Mental Health*.

	Self-reported health	Mental Health
Pooled Logit (Lag Self-employment, Lag Health)		
Univariate regression	0.11** (0.04)	0.07 (0.04)
+ Demographic controls	0.08* (0.04)	-0.00 (0.04)
+ Employment controls	0.08* (0.04)	0.00 (0.04)
N, person-year observations	30,918	23,600
N, individuals	9,970	8,315
Fixed Effect Logit		
Univariate regression	0.01 (0.09)	-0.06 (0.09)
+ Demographic controls	0.01 (0.09)	-0.06 (0.09)
+ Employment controls	0.02 (0.09)	-0.06 (0.09)
N, person-year observations	20,909	20,323
N, individuals	4,502	4,718
Bivariate Probit		
$\rho = 0.00$	0.06*** (0.01)	0.02 (0.02)
$\rho = 0.10$	-0.10*** (0.01)	-0.14*** (0.02)
$\rho = 0.20$	-0.26*** (0.01)	-0.30*** (0.02)
Equal selection	-0.14*** (0.01)	-0.20*** (0.02)
N, person-year observations	44,930	35,649
N, individuals	12,247	10,723

Note: Standard errors in parentheses and clustered per individual; Standard errors in the bivariate probit model are based on 250 bootstrap replications; $^{*}p < 0.05$. $^{**}p < 0.01$. $^{***}p < 0.001$.

[12] We repeated the pooled logit analyses without the lagged dependent variable using only the person-year observations from the analyses with the lagged dependent variable. The regression results are qualitatively the same as those presented inTable 7.2.

As argued by Granger (1969), the explanatory power of self-employment for future realizations of health implies a form of causality. However, this type of causality cannot distinguish between a contextual effect of self-employment on health and third factors influencing both self-employment and health. We use a fixed-effects logit regression to control for unobserved heterogeneity deriving from possible time-invariant third factors influencing both self-employment and health. Examples of such variables could be risk aversion, time preferences, and genetic factors. A significant association between self-employment and health that remains after controlling for fixed unobserved determinants of self-employment and health, would be consistent with a contextual effect of self-employment on health. Because time-invariant variables are accounted for in the fixed effect, we only control for *Self-employment* and time-varying control variables in our three model specifications.

The results of the fixed-effects panel regressions are in panel 2 of Table 7.3. Note that the sample size is somewhat smaller here because in the fixed-effects logit regression, the individuals without a change in the dependent variable are dropped.[13] The associations for *Self-reported Health* and *Mental Health* with *Self-employment* are not significant. Hence, changes in *Self-reported Health* and *Mental Health* do not appear to be related to changes in *Self-employment*. We consider this result as evidence against a contextual effect of self-employment on health. It also suggests that unobserved time-invariant individual characteristics influence both self-employment and health and that the positive association between self-employment and health mainly reflects a "selection effect" in which intrinsically healthier individuals select into self-employment.

An additional piece of evidence for a selection effect comes from the inclusion of higher-order lags of self-employment into the univariate pooled logit regressions. The coefficients for higher-order lags of self-employment remain similar in size as those presented in Table 7.2 and statistically significant at the five-percent level up to the fourth (*Self-reported Health*) and second lag (*Mental Health*), which would be counterintuitive if self-employment were to cause good health. Rather, these results suggest that the coefficient for *Self-employment* picks up the effect of unobserved time-invariant individual characteristics that are associated with better health.

7.4.3 Pooled Regressions Controlling for Unobservables

The fixed-effect logit model has two limitations. First, the model only controls for time-invariant third factors, while time-varying factors influencing both health and self-employment could also play a role. Second, the coefficients are only identified based on

[13] A fixed-effect OLS regression that includes all available person-year observations gives qualitatively the same results. Moreover, the pooled logit results from Table 7.2 remain qualitatively the same if the regression analyses are restricted to the person-year observations that are included in the fixed-effect logit regressions.

individuals who switch between self-employment and wage work. Such a switch is relatively rare (less than five percent between every two wave), resulting in a small and possibly non-random sample if switching is induced by time-varying factors that are not controlled for. To reduce this concern, we also implement a method proposed by Altonji et al. (2005) that uses the selection on observable variables as an indication for the potential selection on unobservable variables. Essentially, their idea is that it is unlikely that by controlling for the observed individual characteristics available in the dataset, all factors influencing both self-employment and health are controlled for. There will always be unobserved factors affecting decisions with respect to health and self-employment. However, the authors argue that the observed characteristics available in the dataset are typically carefully chosen, such that the selection of observable characteristics can be seen as an upper bound to the selection based on unobservable characteristics.

Specifically, Altonji et al. (2005) suggest using a bivariate probit model to quantify how large the selection on the basis of unobservable variables into self-employment would have to be to fully account for the association between self-employment and health. Their suggested model depends on an assumption about the correlation ρ between the error components in the equations for self-employment and health.[14] Altonji et al. (2005) additionally suggest estimating a "worst-case" scenario where it is assumed that the selection on observable variables is equal to the selection on unobservable variables, which places a particular constraint on the value of ρ in the estimation of the bivariate probit model (see Altonji et al., 2005 for details). This scenario creates an alternative way to gauge the plausibility of a contextual effect of self-employment on health without the need to rely solely on individuals switching jobs.

The bivariate probit results are given in the bottom panel of Table 7.3. These regressions include both the demographic and employment controls. Obviously, in the models where we impose $\rho = 0$, we obtain qualitatively the same results as those presented in Table 7.2 because both models correspond to running separate probit/logit regressions for health and self-employment. When we constrain and increase the correlation between the error components in the health and self-employment regressions ($\rho = 0.10$, $\rho = 0.20$), the coefficient for *Self-employment* becomes strongly significant in the opposite direction. This result suggests that a relatively small correlation between the error components (unobserved factors) of self-employment and health already accounts for the entire positive association, and in fact even turns it negative.

[14] The equations take the form $E = \mu + \gamma X + \eta$ and $H = \alpha + \beta E + \tau X + \varepsilon$, where individual subscripts are omitted, E is self-employment, and X are the observed characteristics, H represents health, and η and ε are the error terms for self-employment and health, respectively. The correlation between these error terms is typically denoted by ρ in the bivariate probit model.

However, in practice, we do not know the value of ρ. We therefore also present the "worst case" scenario, where the selection on observable variables is assumed to be similar to the selection on unobservable variables. Under this scenario, the parameter ρ is estimated to be 0.12 for *Self-reported Health* and 0.16 for *Mental Health*. These positive correlations indicate that the unobserved factors influencing self-employment and health are positively correlated, which implies that healthier individuals are more likely to become self-employed. Imposing this restriction on ρ, the coefficients for *Self-employment* are in both models negative and significant (Table 7.3, bottom panel). The results thus confirm that, as in the fixed-effects regressions, if selection on unobserved variables is considered, the positive cross-sectional association between self-employment and health disappears.

In fact, the association even becomes negative, which would suggest a negative effect of self-employment on health. Because these latter results depend on a subjective judgment on the importance of unobserved explanatory variables in the regressions, we see these results as complimentary to the fixed-effect panel regression outcomes, which showed no contextual effect of self-employment on health. Altogether, in our view, the results provide compelling evidence that the contextual effect of self-employment on health is non-positive, possibly zero, and, if anything, negative

7.5 Robustness Checks

In this section we discuss a number of analyses performed to gauge the robustness of our findings. First, we investigated whether health-related attrition out of work was different between the self-employed and wage workers. We estimated a pooled logit model explaining the probability of not working in the next wave by self-employment, current health and the interaction between self-employment and current health. We find that this interaction term is not significant at the five-percent level for *No Health Conditions*, *Self-reported Health*, and *Mental Health*. This result suggests that health-related attrition out of work is not different across the self-employed and wage workers.

For consistency across methods we dichotomized our three dependent variables, which unavoidably requires introducing an arbitrary threshold. We tested the sensitivity to this dichotomization in two different ways. First, when estimating ordered logit regressions rather than binary logit regressions, the initial association between self-employment and our three health outcomes exists and is similar in magnitude to the one presented in Table 7.2. Second, we varied the thresholds in the dichotomization. For *No Health Conditions*, if we place the threshold on the 9-point scale between 1 and 2, and between 2 and 3, we get a significant coefficient of 0.16 and 0.14, respectively, very much in line with the base result. Imposing the threshold higher on the scale is difficult, because less than 3% of the sample has more than 3 diseases. For *Self-reported Health*, if we place the threshold between Excellent and Very Good we get a significant coefficient of 0.29. Interestingly, the coefficient

for *Self-employment* is not significant if the threshold lies between Good and Fair. While this may partly due to lack of power (the bad health group in this analysis is only 13%), it suggests that the association mainly reflects a disproportionate fraction of self-employed reporting their health to be "Very good" and "Excellent". Placing the threshold for dichotomization on the 9-point CESD scale for mental health between 1 and 2, between 2 and 3, and between 3 and 4 gives a coefficient of 0.07, 0.09, and 0.12 for *Self-employment*, respectively (only the latter is significant). Less than 7% of the person-year observations have more than 4 depression symptoms.

We also looked at other, more indirect, health measures available in the dataset, to investigate the consistency of the reported findings and to get a better impression of the mechanisms involved. As alternative, more physical health measures, we selected *Overweight* (BMI > 25), *Obese* (BMI > 30), and *Back problems* (1/0). We find that *Self-employment* is negatively associated with *Overweight* ($p = 0.04$) and *Obese* ($p = 0.05$), but not associated with having back problems ($p = 0.56$). The HRS also asks respondents whether *Health limits work* (1/0), which we find to be positively associated with self-employment ($p < 0.01$). This corroborates our main finding that self-employment does not strongly affect one's health, but rather that health is a strong determinant of self-employment decisions. Rather than exiting the labor force completely, less healthy individuals may decide to become self-employed if they cannot find wage-work.

7.6 Conclusion

It is notoriously difficult to discriminate between a contextual effect of self-employment on health and health-related selection of individuals into self-employment. However, this discrimination is a prerequisite for health policy development concerning this quantitatively and qualitatively important part of the labor force. Therefore, we use several methods to distinguish between these two effects. We find the self-employed to be generally healthier than wage workers, both in terms of subjective health outcomes as well as in more objective outcomes such as the absence of chronic conditions. While it is tempting to attribute these results to the high level of job control and to even consider self-employment as a viable alternative to health-induced early retirement, our results suggest that the health differences are explained by a selection effect, in which healthier individuals self-select into self-employment.

This main conclusion is supported by the absence of a statistically significant effect of self-employment on health in fixed-effects regressions, which suggests that time-invariant individual characteristics influence both self-employment and health. Additionally, applying methods proposed by Altonji et al. (2005) suggests that it only takes a relatively small amount of selection based on unobserved characteristics into self-employment and health to fully account for the positive association between the two. These results are in line with

the two-time periods, females only, study on the relation between self-employment and health by Dolinksy & Caputo (2003).

Our results not only emphasize the importance of a selection of comparatively healthier individuals into self-employment but also provide suggestive evidence that the contextual effect of self-employment on health, if anything, is negative. This conclusion is, however, tentative and based upon relatively strong assumptions on the amount of selection on the basis of unobserved individual characteristics. Nonetheless, the results do show that health does not seem to be a non-monetar benefit of self-employment as was proposed by Stephan & Roesler (2010).In fact, the influence of self-employment is potentially even negative.

Further research is also needed to identify the factors influencing both self-employment and health. Apart from traditional and more obvious variables such as risk-aversion and perseverance, a recent line of inquiry has stressed the role of genes. Self-employment is to a certain extent influenced by genetic factors (Nicolaou et al., 2008a; Van der Loos et al., 2013b). It is perceivable that the same genetic factors influence both self-employment and health (such a mechanism is called pleiotropy in genetics). Although it falls outside the scope of this paper to reveal these and other joint causal factors, the possible finding of a shared causal factor for self-employment and health would be a major breakthrough.

Awareness of the presence of the selection mechanism is important for both policy makers and individuals who consider becoming self-employed. Stimulating self-employment is a key objective in many countries due to its assumed contribution to economic growth. The existence of entrance barriers may prevent such a policy to be successful. Our results indicate that health status may be such a barrie. Since we cannot distinguish between health itself and correlates of health (such as expected health or health of a spouse), future research should further disentangle the selection mechanism to establish whether health status is a perceived barrier (the less healthy do not even try to become self-employed) or an actual barrier (the less healthy are faced with more obstacles, such as in the process of securing loans, when they want to start a business).

CHAPTER 8

Entrepreneurship, Laterality and Dyslexia

Based on Hessels, Rietveld, & Van der Zwan (2014).

Abstract

The supposed creativity of left-handed and dyslectic individuals may fit well with an entrepreneurial career for which the development of novel and useful ideas is of fundamental importance. Dyslectic individuals may also choose for entrepreneurship in the absence of other relevant employment options. There is indeed ample anecdotal evidence of (famous) left-handed and dyslectic entrepreneurs. Empirical evidence from two representative Dutch samples, however, shows that dyslectic and left-handed individuals are not more likely to be(come) entrepreneurs than non-dyslectic and right-handed individuals.

8.1 Introduction

A large literature has addressed the issue of why individuals choose to become an entrepreneur as opposed to an employee (Parker, 2009). Occupational choice theory presumes that people decide to become entrepreneurs if their total expected utility from entrepreneurship (e.g. through earnings, independence, or work satisfaction) is higher than the utility they expect to derive from their best alternative employment option (Taylor, 1999). This coincides with the notion that utility is high if there is a high "person-job fit" meaning that an individual's characteristics match well with the requirements of the job (Kristof-Brown, Zimmerman, & Johnson, 2005).

Creativity and alertness to opportunities are thought to be fundamental characteristics of entrepreneurs (Kirzner, 1973), because an important task of them is to come up with novel and useful business ideas (Ward, 2004). Left-handed individuals are typically characterized by thinking differently and coming up with creative solutions (Newland, 1981). Hand laterality may therefore determine economic outcomes and socio-economic status, for example in terms of earnings (Denny & O'Sullivan, 2007; Ruebeck, Harrington, & Moffitt, 2007; Faurie et al., 2008, 2012). Specifically, left-handed individuals may derive a higher expected utility from entrepreneurship and, hence, may be more inclined to become entrepreneurs than right-handed individuals. People point to examples such as Henry Ford and Bill Gates as famous left-handed entrepreneurs. The present chapter investigates the relationship between left-handedness and entrepreneurship in a rigorous way by using a representative sample of the Dutch adult population.

Dyslexia has been linked to creativity as well (Everatt, Steffert, & Smythe, 1999; Denny & O'Sullivan, 2007). Dyslectic individuals may have become used to finding creative solutions through the experience of situations in which they are disadvantaged and perseverance is required. Furthermore, the literature on entrepreneurship as an occupational choice emphasizes the importance of the opportunity costs of entrepreneurship. Individuals who face lower opportunity costs are more likely to become entrepreneurs (Hamilton, 2000). Dyslectic individuals may face low opportunity costs because of relatively few alternative employment options, or experience difficulties in finding a job in paid employment. Therefore, dyslectic individuals may derive a higher expected utility from entrepreneurship than from paid employment. There are examples of well-known entrepreneurs who are dyslectic such as Richard Branson, Henry Ford, and Steve Jobs. A descriptive study by Logan (2009) concludes that entrepreneurs are more often dyslectic than corporate managers.

The above arguments support the claim that left-handed and dyslectic individuals would be more inclined to be entrepreneurs. However, we have not observed any evidence that is based on representative samples of a country's underlying adult population. This article uses two representative samples from the Netherlands to contribute to the literature

on entrepreneurship as an occupational choice by investigating the relationships between hand laterality, dyslexia, and entrepreneurship. Our empirical results do not support the claim that left-handed individuals are more likely to be an entrepreneur than right-handed individuals. Neither do we find support for the notion that the incidence of entrepreneurship is higher among dyslectic individuals than non-dyslectic individuals.

8.2 Data

8.2.1 Samples

To study the relationship between left-handedness and entrepreneurship we use the Longitudinal Internet Studies for the Social Sciences (LISS) panel dataset (Scherpenzeel, 2011). The LISS panel data were collected by CentERdata (Tilburg University, The Netherlands) through its MESS project funded by the Netherlands Organization for Scientific Research. The members of this dataset were recruited from May until December 2007 by drawing a representative sample of 10,150 households of the Dutch speaking population permanently living in the Netherlands. Respondents are followed over time by asking them each year online questions about several themes. The third wave of data collection (2010) is used for our analysis because people were then asked about their hand laterality.

To investigate the association between dyslexia and entrepreneurship, we use the Dutch data from the Global Entrepreneurship Monitor (GEM) 2013. GEM started in 1999 and has expanded to a collaboration of almost 70 countries in 2013. GEM consists of an adult population survey that collects information about entrepreneurial activity and its many facets in the Netherlands and all other participating countries. The Dutch 2013 sample contains about 2,000 individuals working as an entrepreneur and/or employee aged between 18 and 65. The Dutch GEM data were collected by Panteia (Zoetermeer, the Netherlands). We use data for 2013 for the Netherlands because in this year and in this country only questions on reading ability were included in the GEM survey. Interviews with randomly selected individuals were conducted in April and May 2013 via fixed-line (37%) or mobile telephone (63%).[15]

8.2.2 Entrepreneurship Measures

The most often used proxy for entrepreneurship is self-employment (Parker, 2009). The definition used differs slightly between the LISS and the GEM dataset. In the LISS framework one is asked about his/her main occupation. An individual is considered to be self-employed if (s)he is (or was in his/her last job) self-employed, freelancer, independent professional, director of a limited liability or private limited company, or a majority share-

[15] All analyses with the GEM data are reweighted by gender, age and education to make the sample representative along these dimensions of the underlying Dutch population.

holder director. Someone is in paid employment if (s)he is (or was in his/her last job) an employee in temporary or permanent paid employment, an on-call employee, or temp-staffer. The GEM survey asks individuals about their occupational status where the relevant options are self-employment and (full-time or part-time) paid employment. There is a possibility of part-time self-employment when individuals are self-employed and have a full-time or part-time job in paid employment at the same time. Such individuals are considered to be self-employed in our analyses.[16]

For our analysis on the relationship between dyslexia and entrepreneurship, we use additional dependent variables because of the richness of the GEM dataset in the area of entrepreneurship. That is, a second dependent variable *business ownership* refers to individuals who own and manage (alone or with others) a business. A third dependent variable *total early-stage entrepreneurship* (TEA) is generated. TEA contains individuals who are trying to start a business (nascent entrepreneurs) and owner-managers of businesses that have been in existence for less than 42 months. TEA has been used often in the GEM framework to compare countries on basis of this dynamic measure of entry into entrepreneurship or new entrepreneurial activity.

8.2.3 Left-handedness and Dyslexia Measures

The LISS panel dataset simply asks individuals whether they are left-handed or right-handed. There is no category for ambidexterity. The core GEM questionnaire does not contain questions about an individual's reading ability. For the present study we included such questions in the Dutch 2013 questionnaire. Specifically, information about dyslexia is retrieved by asking respondents the following question: "Is your reading achievement substantially below that expected given your age, intelligence, and education?" This definition corresponds with the first-listed criterion for "reading disorder" (dyslexia) as defined in the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) of the American Psychiatric Association (2000).[17] A second question to allow for a broader definition of dyslexia was asked to include individuals whose reading achievement has improved over time, but who experienced a lower achievement in the past: "Has your reading achievement ever been diminished in the past?"

[16] The results are qualitatively similar when individuals who combine self-employment with full-time or part-time paid employment are included in the group of employees instead of self-employed individuals.

[17] This exact definition reads as follows (p. 53): "Reading achievement, as measured by individually administered standardized tests of reading accuracy or comprehension, is substantially below that expected given the person's chronological age, measured intelligence, and age-appropriate education."

8.2.4 Control Variables

For both research questions, the same set of control variables is used. These control variables have been included frequently in earlier studies on the determinants of self-employment or entrepreneurship. An overview of these control variables and the (in)dependent variables used in the present study is provided in Table 8.1.

Table 8.1. Definitions of dependent, independent, and control variables.

Dependent variable	
Self-employment	1 if self-employed, 0 if in paid employment
Business ownership (GEM only)	1 if business owner, 0 if in paid employment
Total early-stage entrepreneurial activity (TEA; GEM only)	1 if early-stage entrepreneur, 0 if in paid employment
Independent variables	
Left-handedness	1 if left-handed, 0 if right-handed
Dyslexia (strict definition)	1 if yes to "Is your reading achievement substantially below that expected given your age, intelligence, and education?", 0 if no
Dyslexia (broad definition)	1 if yes to "Is your reading achievement substantially below that expected given your age, intelligence, and education?" or yes to "Has your reading achievement ever been diminished in the past?", 0 if no to both
Control variables	
Male	1 if male, 0 if female
Age	Integer value between 18 and 65
Education	1: Lower secondary education or primary/no education (reference) 2: Higher secondary education 3: Intermediate vocational education 4: Higher vocational education 5: University
Household size	Integer value between 1 and 5 (value 5 also represents larger household sizes)
Household income (gross yearly)	1: Less than 30,000 euro (reference) 2: Between 30,000 and 60,000 euro 3: More than 60,000 euro 4: Not answered/don't know (missing values)
Born in the Netherlands	1 if born in the Netherlands, 0 if born in another country
Urbanization	LISS: 1 if respondent lives in a place with more than 1,500 addresses per km^2, 0 otherwise; GEM: 1 if respondent lives in one of the three largest cities of the Netherlands (Amsterdam, Rotterdam, The Hague), 0 otherwise

8.3 Results

8.3.1 Left-handedness

Descriptive analyses reveal that the incidence of left-handedness in the Dutch population from 18 to 65 years is 11.1%.[18] On basis of Chi-squared tests we conclude that men are more likely to be left-handed than women (p-value < 0.05), and that the associations between left-handedness and the other control variables are insignificant. Furthermore, left-handed and right-handed individuals are equally likely to be self-employed (p > 0.05). Table 8.2 shows the estimated average marginal effects for the binary logit regression with self-employment versus paid employment as the dependent variable and left-handedness as the independent variable. This multiple regression framework reveals that left-handed individuals are not more likely to be self-employed than right-handed individuals (p > 0.05).

Table 8.2. Binary logit regression for left-handedness with self-employment versus paid employment as the dependent variable. Marginal effects (ME) with standard errors (SE) are reported.

	Self-employment	
	ME	SE
Predicted probability	0.089***	0.005
Left-handedness	-0.002	0.015
Male	0.018	0.011
Age	0.003***	0.000
Education: Higher secondary education	0.023	0.019
Education: Intermediate vocational educ.	0.012	0.012
Education: Higher vocational education	0.020	0.014
Education: University	0.065**	0.023
Household size	0.006	0.004
Income: 30,000-60,000 euro	-0.021	0.012
Income: > 60,000 euro	0.023	0.025
Income: Missing	0.079**	0.030
Born in the Netherlands	-0.005	0.019
Urbanization	-0.026*	0.010
Number of observations	3,319	
Log likelihood	-952.658	
Pseudo R^2	0.043	

Note: LISS data for the Netherlands, wave 3 (2010); * p < 0.05, ** p < 0.01, *** p < 0.001. Reference categories are "Lower secondary education or primary/no education" (Education) and "< 30,000 euro" (Income).

[18] Papadatou-Pastou, Martin, Munafò, & Jones (2008) find in a large meta-analysis an incidence of left-handedness between 10% and 12%.

8.3.2 Dyslexia

The incidence of dyslexia among the Dutch population from 18 to 65 years is estimated at 8.8%.[19] Chi-squared tests show that dyslectic relative to non-dyslectic individuals (using the strict definition) are male, are less educated, have a lower household income, and are less likely to be born in the Netherlands (p-values < 0.05). Furthermore, dyslectic individuals are more likely to be an early-stage entrepreneur versus an employee (16.9% versus 11.8%; $p < 0.10$); the differences in terms of self-employment and business ownership are not statistically different at any reasonable significance level. Table 8.3 shows the corresponding binary logit estimation results (average marginal effects and their standard errors). Three different dependent variables are used: being self-employed versus an employee (Model 1), being a business owner versus an employee (Model 2), and being involved in total early-stage entrepreneurial activity versus an employee (TEA; Model 3).

The general conclusion is that individuals with dyslexia are not more likely to be self-employed or a business owner. We find some indication that individuals with dyslexia are more likely to be involved in early-stage entrepreneurial activity, but this relationship is significant at the 10% level. Replacing the strict definition with the broad definition of dyslexia (see Table 8.1) leads to insignificant associations as well (p-values > 0.05).[20] To control for the fact that individuals are able to handle their below-average reading achievement to a certain extent, the following question was also asked in the Dutch GEM survey: "Have you ever had professional counseling and/or treatment to improve your reading achievement?" Including this control variable to the model specifications in Table 8.3 does not lead to qualitatively different results. Finally, we add a category to our dyslexia variable indicating whether an individual's below-average reading ability has hindered him/her to find a job. Again, the results remain similar.

[19] According to the broad definition, this is 13.8%. Incidence rates of dyslexia/reading disability vary considerably in the literature, depending on the definition used.

[20] The estimated marginal effects for this broad definition of dyslexia (with standard errors between parentheses) are 0.005 (0.029), 0.009 (0.027), and 0.014 (0.023) for self-employment, business ownership, and early-stage entrepreneurial activity, respectively.

Table 8.3. Binary logit regressions for dyslexia with entrepreneurship versus paid employment as dependent variable. Marginal effects (ME) with standard errors (SE) are reported.

	Self-employment (1)		Business ownership (2)		Total early-stage entrepreneurial activity (3)	
	ME	SE	ME	SE	ME	SE
Predicted probability	0.202***	0.009	0.162***	0.008	0.115***	0.007
Dyslexia (strict definition)	0.047	0.037	0.041	0.036	0.053	0.031
Male	0.099***	0.018	0.077***	0.016	0.049**	0.014
Age	0.004***	0.001	0.004***	0.001	-0.001	0.001
Education: Higher secondary education	0.049	0.043	0.040	0.039	0.066	0.037
Education: Intermediate vocational educ.	0.027	0.024	0.033	0.022	0.033	0.019
Education: Higher vocational education	0.045	0.027	0.056*	0.025	0.060**	0.022
Education: University	0.129**	0.038	0.120**	0.036	0.115***	0.033
Household size	0.024***	0.007	0.020**	0.006	0.012*	0.006
Income: 30,000-60,000 euro	-0.003	0.023	0.008	0.021	-0.001	0.018
Income: > 60,000 euro	0.026	0.028	0.030	0.026	0.047	0.025
Income: Missing	0.070	0.040	0.070	0.037	0.052	0.034
Born in the Netherlands	0.003	0.038	0.004	0.035	-0.024	0.034
Urbanization	0.011	0.030	0.013	0.027	0.027	0.024
Number of observations	2,039		2,004		1,941	
Log likelihood	-960.310		-827.884		-649.951	
Pseudo R^2	0.049		0.050		0.045	

Note: Global Entrepreneurship Monitor data for the Netherlands (2013); * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Reference categories are "Lower secondary education or primary/no education" (Education) and "< 30,000 euro" (Income).

8.4 Discussion and Conclusion

Left-handed and dyslectic individuals have characteristics that fit with an entrepreneurial occupation. Furthermore, dyslectic individuals may face difficulty in finding and accommodating to a job in paid employment. We demonstrate, however, the absence of a significant association between the likelihood of becoming an entrepreneur versus an employee and being left-handed or dyslectic in two Dutch population-based samples. Despite the numerous examples of successful left-handed and dyslectic entrepreneurs, it can not be empirically substantiated on the population level that entrepreneurship is a particularly suitable career choice for left-handed or dyslectic individuals.

Summary

Economists have always been adept at integrating ideas and concepts from other scientific fields into their own research agenda. This thesis adopts a perspective in which individual economic choices and outcomes are connected to individual biological characteristics. Thus, this thesis contains research on the intersection of economics and biology, an interdisciplinary field that is called 'biological economics'.

This thesis starts with an introductory chapter that motivates hybrid research of economics and biology. First, knowledge about biological predispositions to economic choices and outcomes improves our understanding of the causes and consequences of individual differences. Second, biological measures known to be associated with economic choices and outcomes could be used in (otherwise non-biological) empirical work as control variables or instrumental variables. Third, information about economic predisposition to biological states and outcomes may result in targeted interventions to prevent undesired outcomes.

The next seven chapters address three economic measures: educational attainment, subjective well-being and entrepreneurship. They also address four biological measures: genes, health, dyslexia, laterality. First, the genetic architecture of educational attainment, subjective well-being and entrepreneurship is investigated. Next, the influence of entrepreneurship on health and the correlation between entrepreneurship, dyslexia and laterality is analyzed.

This thesis finds that genetic variants explain an important part of the population variance in educational attainment, cognitive function, subjective well-being and entrepreneurship. Moreover, specific genetic variants associated with educational attainment, cognitive function and entrepreneurship are identified. This thesis finds also that entrepreneurs are generally healthier than wage-workers, and that the selection of comparatively healthier individuals into entrepreneurship accounts for the positive cross-sectional association. Finally, it provides empirical evidence that dyslectic and left-handed individuals are not more likely to be(come) entrepreneurs than non-dyslectic and right-handed individuals.

Although the full breakthrough of *biological economics* still remains, the expected value of research on the intersection of economics and biology is argued to be high. It is reasonable to assume that the interest in biological economics will only grow in the coming years. This thesis makes only some contributions to the field, but does show how a collaborative confrontation between economics and biology within an interdisciplinary team yields high quality research.

Samenvatting (Summary in Dutch)

Economen integreren graag ideeën en concepten uit andere wetenschappelijk disciplines in hun eigen onderzoek. Dit proefschrift verbindt individuele economische keuzes en uitkomsten aan individuele biologische eigenschappen. De opstellen in dit proefschrift dragen bij aan een interdisciplinair onderzoeksveld dat ook wel 'biologische economie' wordt genoemd.

Dit proefschrift begint met een introductie waarin het nut van onderzoek op het kruispunt van economie en biologie wordt beschreven. Allereerst geeft kennis over biologische predisposities van economisch gedrag meer inzicht in de oorzaken en gevolgen van individuele verschillen. Ten tweede kunnen biologische kenmerken die geassocieerd zijn met economische kenmerken gebruikt worden voor (mogelijk niet-biologisch) empirisch werk als controle variabele of instrumentele variabele. Ten derde geeft kennis over een causaal verband tussen economisch gedrag en de biologische staat van een individu de mogelijkheid om doelgericht in te grijpen om ongewilde uitkomsten te voorkomen.

De volgende zeven hoofdstukken gaan over drie economische maatstaven: opleidingsniveau, subjectief welzijn en ondernemerschap. Deze worden verbonden aan vier biologische kenmerken: genen, gezondheid, dyslexie en linkshandigheid. Allereerst wordt de genetische architectuur van opleidingsniveau, cognitief functioneren, subjectief welzijn en ondernemerschap onderzocht. Vervolgens wordt de invloed van ondernemerschap op gezondheid en de samenhang tussen ondernemerschap, dyslexie en linkshandigheid bestudeerd.

Dit proefschrift laat zien dat genetische varianten een belangrijk deel van de populatievariantie in opleidingsniveau, cognitief functioneren, subjectief welzijn en ondernemerschap verklaren. Het identificeert zelfs enkele specifieke genetische varianten die geassocieerd zijn met opleidingsniveau, cognitief functioneren en ondernemerschap. Dit proefschrift laat ook zien dat ondernemers gemiddeld genomen gezonder zijn dan mensen in loondienst. Dit komt doordat gezondere mensen eerder ondernemer worden dan minder gezondere mensen. Verder wordt er empirische aangetoond dat dyslectische en linkshandige mensen niet vaker ondernemer zijn of worden dan niet-dyslectisch of rechtshandige mensen.

Hoewel de volledige doorbraak van *biologische economie* nog uitstaat, is het nut van onderzoek op het kruispunt van economie en biologie erg hoog. Het is daarom aan te nemen dat de interesse in biologische economie enkel zal toenemen in de komende jaren. Dit proefschrift levert slechts enkele bijdragen aan het onderzoeksgebied, maar het laat wel zien dat een samenwerking (die tegelijkertijd een confrontatie is) tussen economie en biologie in een interdisciplinair team wetenschappelijk onderzoek oplevert van hoge kwaliteit.

References

Abdellaoui, A., Hottenga, J. J., De Knijff, P., Nivard, M. G., Xiao, X., Scheet, P., … Boomsma, D.I. (2013). Population structure, migration, and diversifying selection in the Netherlands. *European Journal of Human Genetics*, *21*, 1277-1285.

Adams, P., Hurd, M. D., McFadden, D., Merrill, A., & Ribeiro, T. (2003). Healthy, wealthy, and wise? Tests for direct causal paths between health and socioeconomic status. *Journal of Econometrics*, *112*, 3-56.

Adler, N. E., Boyce, T., Chesney, M. A., Cohen, S., Folkman, S., Kahn, R. L., & Syme, S. L. (1994). Socioeconomic status and health: The challenge of the gradient. *American Psychologist*, *49*, 15–24.

Altonji, J. G., Elder, T. E., & Taber, C. R. (2005). Selection on observed and unobserved variables: Assessing the effectiveness of Catholic schools. *Journal of Political Economy*, *113*, 151-184.

American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders. Fourth edition, text revision (DSM-IV-TR)*. Washington, DC, USA: American Psychiatric Association.

Argyle, M. (1997). Is happiness a cause of health? *Psychology , & Health*, *12*, 769–781.

Audretsch, D., & Keilbach, M. (2004). Entrepreneurship capital and economic performance. *Regional Studies*, *38*, 949–959.

Audretsch, D. B., & Thurik, A. R. (2000). Capitalism and democracy in the 21st century: From the managed to the entrepreneurial economy. *Journal of Evolutionary Economics*, *10*, 17-34.

Audretsch, D. B., & Thurik, A. R. (2001). What is new about the new economy: Sources of growth in the managed and entrepreneurial economies. *Industrial and Corporate Change*, *10*, 267-315.

Bang, R. H. (2010). Happiness in behaviour genetics: Findings and implications. *Journal of Happiness Studies*, *11*, 369–381.

Barrett, J. C., & Cardon, L. R. (2006). Evaluating coverage of genome-wide association studies. *Nature Genetics*, 38, 659–662.

Bartels, M., Saviouk, V., De Moor, M. H., Willemsen, G., Van Beijsterveldt, T. C., Hottenga, J. J., … Boomsma, D. I. (2010). Heritability and genome-wide linkage scan of subjective happiness. *Twin Research and Human Genetics*, *13*, 135–142.

Bartels, M., & Boomsma, D. I. (2009). Born to be happy? The etiology of subjective well-being. *Behavior Genetics*, *39*, 605–615.

Beauchamp, J. P., Cesarini, D., Johannesson, M., Van der Loos, M. J. H. M., Koellinger, P. D., Groenen, P. J. F., … Christakis, N. A. (2011). Molecular genetics and economics. *Journal of Economic Perspectives*, *25*, 57–82.

Beck, T., & Demirguc-Kunt, A. (2006). Small and medium-size enterprises: Access to finance as a growth constraint. *Journal of Banking , & Finance*, *30*, 2931–2943.

Benjamin, D. J., Cesarini, D., Chabris, C. F., Glaeser, E. L., Laibson, D. I., Guðnason, V., … Lichtenstein, P. (2012a). The promises and pitfalls of genoeconomics. *Annual Review of Economics*, *4*, 627–662.

Benjamin, D. J., Cesarini, D., Van der Loos, M. J. H. M., Dawes, C. T., Koellinger, P. D., Magnusson, P. K. E., … Visscher, P. M. (2012b). The molecular genetic architecture of economic and political preferences. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 8026–8031.

Benyamin, B., Pourcain, B., Davis, O. S., Davies, G., Hansell, N. K., Brion, M.-J., … Visscher, P. M. (2014). Childhood intelligence is heritable, highly polygenic and associated with FNBP1L. *Molecular Psychiatry*, *19*, 253–258.

Beugelsdijk, S., & Noorderhaven, N. (2005). Personality characteristics of self-employed: An empirical study. *Small Business Economics*, *24*, 159-167.

Bjuggren, C. M., Johansson, D., & Stenkula, M. (2012). Using self-employment as proxy for entrepreneurship: Some empirical caveats. *International Journal of Entrepreneurship and Small Business*, *17*, 290-303.

Blanchflower, D. G. (2000). Self-employment in OECD countries. *Labour Economics*, *7*, 471-505.

Bouchard, T. J., & McGue, M. (1981) Familial studies of intelligence: A review. *Science*, 212, 1055–1059.

Bouchard, T. J., & McGue, M. (2003). Genetic and environmental influences on human psychological differences. *Journal of Neurobiology*, *54*, 4–45.

Bowles, S., & Gintis, H. (2002). The inheritance of inequality. *Journal of Economic Perspectives*, *16*, 3–30.

Bradley, D. E., & Roberts, J.A . (2004). Self-employment and job satisfactions: Investigating the role of self-efficacy, depression, and seniority. *Journal for Small Business Management*, *42*, 37–58.

Branigan, A. R., McCallum, K. J., & Freese, J. (2013). Variation in the heritability of educational attainment: an international meta-analysis. *Social Forces*, *92*, 109-140.

Buttner, E. H. (1992). Entrepreneurial stress: Is it hazardous to your health? *Journal of Managerial Issues*, *4*, 223-240.

Calvin, C. M., Deary, I. J., Webbink, D., Smith, P., Fernandes, C., Lee, S. H., … 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*, 42, 699–710.

Cardon, L. R., & Palmer, L. J. (2003). Population stratification and spurious allelic association. *Lancet, 361*, 598–604.

Carlstedt, B. (2000). *Cognitive abilities: Aspects of structure, process and measurement.* Göteborg, Sweden: Acta Universitatis Gothoburgensis.

Carree, M. A., & Thurik, A. R. (2010). The impact of entrepreneurship on economic growth. In: D.B. Audretsch , & Z.J. Acs (Eds), *Handbook of entrepreneurship research* (pp. 557-594). Berlin, Heidelberg, Germany: Springer Verlag.

Cesarini, D., Dawes, C. T., Johannesson, M., Lichtenstein, P., & Wallace, B. (2009a). Genetic variation in preferences for giving and risk taking. *Quarterly Journal of Economics*, *124*, 809–842.

Cesarini, D., Johannesson, M., Lichtenstein, P., Sandewall, Ö., & Wallace, B. (2010). Genetic variation in financial decision making. *Journal of Finance, 65,* 1725–1754.

Cesarini, D., Johannesson, M., Magnusson, P. K. E., & Wallace, B. (2012). The behavioral genetics of behavioral anomalies. *Management Science*, *58*, 21–34.

Cesarini, D., Lichtenstein, P., Johannesson, M., & Wallace, B. (2009b). Heritability of overconfidence. *Journal of the European Economic Association*, *7*, 617–627.

Chabris, C.F. (2007). Cognitive and neurobiological mechanism of the law of general intelligence. In: M.J. Roberts (Ed.), Integrating the mind: Domain general vs. domain specific processes in higher cognition (pp. 449-491). New York, NY, USA: Psychology Press.

Chabris, C. F., Hebert, B. M., Benjamin, D. J. Beauchamp, J. P., Cesarini, D., Van der Loos, M. J. H. M., … Laibson, D. (2012). Most reported genetic associations with general intelligence are probably false positives. *Psychological Science*, *23*, 1314–1323.

Chaturvedi, S., Zyphur, M. J., Arvey, R. D., Avolio, B. J., & Larsson, G. (2012). The heritability of emergent leadership: Age and gender as moderating factors. *Leadership Quarterly*, *23*, 219–232.

Conley, D. (2009) The promise and challenges of incorporating genetic data into longitudinal social science surveys and research. *Biodemography and Social Biology*, *55*, 238–251.

Cooper, C. L., & Marshall, J. (1976). Occupational sources of stress: a review of the literature relating to coronary heart disease and mental ill health. *Journal of Occupational Psychology*, *49*, 11–28.

Cooper, C. L., & Smith, M. (1985). *Job stress and blue collar work*. Chichester, UK: Wiley.

Dahl, M. S., Nielsen, J., & Mojtabai, R. (2010). The effects of becoming an entrepreneur on the use of psychotropics among entrepreneurs and their spouses. *Scandinavian Journal of Public Health*, *38*, 857–863.

Davey Smith, G., & Ebrahim, S. (2003). 'Mendelian randomization': Can genetic epidemiology contribute to understanding environmental determinants of disease? *International Journal of Epidemiology*, *32*, 1–22.

Davies, G., Harris, S. E., Reynolds, C. A., Payton, A., Knight, H. M., Liewald, D. C., ... Deary, I. J. (2014). A genome-wide association study implicates the APOE locus in nonpathological cognitive ageing. *Molecular Psychiatry*, *19*, 76–87.

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

Deary, I. J., Strand, S., Smith, P., & Fernandes, C. (2007). Intelligence and educational achievement. *Intelligence*, *35*, 13−21.

Deelen, J., Beekman, M., Uh, H. W., Broer, L., Ayers, K. L., Tan, Q., ... Slagboom, P. E. (2014). Genome-wide association meta-analysis of human longevity identifies a novel locus conferring survival beyond 90 years of age. Human Molecular Genetics. Advance online publication. doi: 10.1093/hmg/ddu139

De Moor, M. H. M., Costa, P. T., Terracciano, A., Krueger, R. F., De Geus, E. J. C., Toshiko, T., … Boomsma, D. I. (2012). Meta-analysis of genome-wide association studies for personality. *Molecular Psychiatry*, *17*, 337–349.

De Neve J. E. (2011). Functional polymorphism (5-HTTLPR) in the serotonin transporter gene is associated with subjective well-being: Evidence from a U.S. nationally representative sample. *Journal of Human Genetics*, *56*, 456–459.

De Neve, J. E., Christakis, N. A., Fowler, J. H., & Frey, B.S. (2012). Genes, economics, and happiness. *Journal of Neuroscience, Psychology, and Economics*, *5*, 193–211.

Denny, K., & O'Sullivan, V. (2007). The economic consequences of being left-handed: some sinister results. *Journal of Human Resources*, *42*, 353-374.

Devlin, B., & Roeder, K. (1999). Genomic control for association studies. *Biometrics*, *55*, 997–1004.

De Zeeuw, E. L., Van Beijsterveldt, C. E. M., Glasner, T. J., Ehli, E. A., Davies, G. E., Hudziak, J. J., ... Boomsma, D. I. (2014). Polygenic scores associated with educational attainment in adults predict educational achievement and attention problems in children. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. Advance online publication. doi:10.1002/ajmg.b.32254

Diener, E. (2000). Subjective well-being. *American Psychologist*, *55*, 34–43.

Diener, E., & Seligman, M.E.P (2004). Beyond money: toward an economy of well-being. *Psychological Science in the Public Interest*, 5, 1–31.

Ding, W., Lehrer, S. F., Rosenquist, J. N., & Audrain-McGovern, J. (2009). The impact of poor health on education: New evidence using genetic markers. *Journal of Health Economics*, *28*, 578–597.

Dolinsky, A. L., & Caputo, R.K. (2003). Health and female self-employment. *Journal of Small Business Management*, *41*, 233-241.

Duncan, L. E., & Keller, M. C. (2011). A critical review of the first ten years of candidate gene-by-environment interaction research in psychiatry. *American Journal of Psychiatry*, *168*, 1041-104.

Ebstein, R. P., Israel, S., Chew, S. H., Zhong, S., & Knafo, A. (2010). Genetics of human social behavior. *Neuron*, *65*, 831–844.

Easterlin, R. A. (2003). Explaining happiness. *Proceedings of the National Academy of Sciences of the United States of America*, *100*, 11176–11183.

Ekelund, J., Johansson, E., Järvelin, M. R., & Lichtermann, D. (2005). Self-employment and risk aversion—evidence from psychological test data. *Labour Economics*, *12*, 649-659.

Emre, S., Ünver, N., Ersoy-Evans, S., Yüzbaşıoğlu, A., Gürakan, F., Gümrük, F., & Karaduman, A. (2010). Molecular analysis of Chanarin-Dorfman syndrome (CDS) patients: Identification of novel mutations in the ABHD5 gene. *European Journal of Medical Genetics*, *53*, 141–144.

Eriksson, N., Macpherson, J. M., Tung, J. Y., Hon, L. S., Naughton, B., Saxonov, S., … Mountain, J. (2010). Web-based, participant-driven studies yield novel genetic associations for common traits. *PLOS Genetics*, *6*, e1000993.

European Commission (2004). *Action plan: The European agenda for entrepreneurship*. Available from: ftp://ftp.cordis.europa.eu/pub/incubators/docs/action_plan_on_entrepreneurship.pdf

Evans, D. S., & Leighton, L. S. (1989). Some empirical aspects of entrepreneurship. *American Economic Review*, *79*, 519–535.

Everatt, J., Steffert, B., & Smythe, I. (1999). An eye for the unusual: Creative thinking in dyslectics. *Dyslexia*, *5*, 28-26.

Faurie, C., Bonenfant, S., Goldberg, M., Hercberg, S., Zins, M. , & Raymond, M. (2008). Socio-economic status and handedness in two large cohorts of French adults. *British Journal of Psychology, 99*, 533-554.

Faurie, C., Llaurensa, V., Hegayc, T. , & Raymonda, M. (2012). Handedness and socioeconomic status in an urban population in Uzbekistan. *Evolution and Human Behavior. 33*, 35-41.

Ferreira, M. A. R. & Purcell, S. M. (2009). A multivariate test of association. *Bioinformatics, 25*, 132–133.

Finkelstein, A., Taubman, S., Wright, B., Bernstein, M., Gruber, J., Newhouse, J.P., ... Oregon Health Study Group (2012). The Oregon health insurance experiment: Evidence from the first year. Quarterly Journal of Economics, 127, 1057-1106.

Fletcher, J. M., & Lehrer, S. F. (2011). Genetic lotteries within families. *Journal of Health Economics*, *30*, 647–659.

Forman-Hoffman, V. L., Richardson, K. K., Yankey, J. W., Hillis, S. L., Wallace, R. B., & Wolinsky, F. D. (2008). Retirement and weight changes among men and women in the Health and Retirement Study. *Journal of Gerontology*, *638*, S146-S153.

Fowler, J. H. & Dawes, C. T. (2013). In defense of genopolitics. *American Political Science Review, 107*, 362-374.

Franz, C. E., Panizzon, M. S., Eaves, L. J., Thompson, W., Lyons, M. J., Jacobson, K. C., ... Kremen, W. S. (2012). Genetic and environmental multidimensionality of well- and ill-being in middle aged twin men. *Behavior Genetics*, *42*, 579–591.

Freeman, J. L., Perry, G. H., Feuk, L., Redon, R., McCarroll, S. A., Altshuler, D. M., … Lee, C. (2006). Copy number variation: New insights in genome diversity. *Genome Research*, *16*, 949–961.

Fuchs, V. R. (1982). Self-employment and labor force participation of older males. *Journal of Human Resources*, *17*, 339-357.

Galesloot, T. E., Van Steen, K., Kiemeney, L. A. L. M., Janss, L. L., & Vermeulen, S. H. (2014). A comparison of multivariate genome-wide association methods. *PLOS ONE*, *9*, e95923.

Garner, C. (2007). Upward bias in odds ratio estimates from genome-wide association studies. *Genetic Epidemiology*, *31*, 288–295.

Gelernter, J., Goldman, D., & Risch, N. (1993). The A1 allele at the D2 dopamine receptor gene and alcoholism. A reappraisal. *Journal of the American Medical Association*, *269*, 1673–1677.

Gibson, G. (2012). Rare and common variants: Twenty arguments. *Nature Genetics*, *13*, 135–145.

Gielnik, M. M., Zacher, H., & Frese, M. (2012). Focus on opportunities as a mediator of the relationship between business owners' age and venture growth. *Journal of Business Venturing*, *27*, 127–142.

Gilbert, B. A., Audretsch, D. B., & McDougall, P. P. (2004). The emergence of entrepreneurship policy. *Small Business Economics, 22*, 313-323.

Goddard, M. (2009). Genomic selection: prediction of accuracy and maximisation of long term response. *Genetica, 136*, 245–257.

Goldberger, A. (1979). Heritability. *Economica*, *46*, 327–347.

Granger, C. W. J. (1969). Investigating causal relations by econometric models and cross-spectral methods. *Econometrica*, *39*, 424-428.

Hahn, E., Spinath, F. M., Siedler, T., Wagner, G. G., Schupp, J., & Kandler, C. (2012). The complexity of personality: Advantages of a genetically sensitive multi-group design. *Behavior Genetics*, *42*, 221–233.

Hamer, D., & Sirota, L. (2000). Beware the chopsticks gene. *Molecular Psychiatry*, *5*, 11–13.

Hamilton, B. H. (2000). Does entrepreneurship pay? An empirical analysis of the returns to self-employment. *Journal of Political Economy*, *108*, 604–631.

Harris, J. R., Pedersen, N. L., Stacey, C., & McClearn, G.E. (1992). Age differences in the etiology of the relationship between life satisfaction and self-rated health. *Journal of Aging and Health*, *4*, 349–368.

Headey, B., Muffels, R., & Wagner, G. G. (2010). Long-running German panel survey shows that personal and economic choices, not just genes, matter for happiness. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 17922–17926.

Hébert, R. F., & Link, A. N. (1989). In search of the meaning of entrepreneurship. *Small Business Economics*, *1*, 39–49.

Heckman, J. J., & Rubinstein, Y. (2001). The importance of noncognitive skills: Lessons from the GED testing program. *American Economic Review*, *91*, 145-149.

Helliwell, J., Layard, R., & Sachs, J., (2012). *World happiness report.* New York, NY, USA: The Earth Institute.

Henneman, P., Aulchenko, Y. S., Frants, R. R., Van Dijk, K. W., Oostra, B. A, & Van Duijn, C. M. (2008). Prevalence and heritability of the metabolic syndrome and its individual components in a Dutch isolate: The Erasmus Rucphen Family study. *Journal of Medical Genetics*, *45*, 572–577.

Hessels, J., Rietveld, C. A., & Van der Zwan, P. W. (2014). Unraveling two myths about entrepreneurs. *Economics Letters*, *122*, 435–438

Hewitt, J. K. (2012). Editorial policy on candidate gene association and candidate gene-by-environment interaction studies of complex traits. *Behavior Genetics*, *42*, 1–2.

Hill, W. G., & Weir, B. S. (2011). Variation in actual relationship as a consequence of Mendelian sampling and linkage. *Genetics Research*, *93*, 47–64.

Hill, W. D., Davies, G., Van de Lagemaat, L. N., Christoforou, A., Marioni, R. E., Fernandes, C. P. D., ... Deary, I. J. (2014). Human cognitive ability is influenced by genetic variation in components of postsynaptic signalling complexes assembled by NMDA receptors and MAGUK proteins. *Translational Psychiatry, 4*, e341.

Hindorff, L. A., MacArthur, J., Morales, J., Junkins, H. A., Hall, P. N., Klemm, A. K., & Manolio, T. A. (2013, May 14). A catalog of published genome-wide association studies. Retrieved from http://www.genome.gov/gwastudies

Hirschhorn, J. N., Lohmueller, K., Byrne, E., & Hirschhorn, K. (2002). A comprehensive review of genetic association studies. *Genetics in Medicine, 4*, 45–61.

Hirshleifer, J. (1977). Economics from a biological viewpoint. *Journal of Law and Economics, 20*, 1-52.

Hirshleifer, J. (1978). Competition, cooperation, and conflict in economics and biology. *American Economic Review, 68*, 238-243.

Hodgson, G. M. (1993). The Mecca of Alfred Marshall. *Economic Journal, 103*, 406-415.

Hofman, A., Breteler, M. M. B., Van Duijn, C. M., Janssen, H. L. A., Krestin, G. P., Kuipers, E. J., … Witteman, J. C. M. (2009). The Rotterdam Study: 2010 Objectives and design update. *European Journal of Epidemiology*, *24*, 553–572.

Hofman, A., Van Duijn, C. M., Franco, O. H., Ikram, M. A., Janssen, H. L. A., Klaver, C. C. W., … Witteman, J. C. M. (2011). The Rotterdam Study: 2012 Objectives and design update. *European Journal of Epidemiology*, *26*, 657–686.

Hoggart, C. J., Clark, T. G., De Iorio, M., Whittaker, J. C., & Balding, D. J. (2008). Genome-wide significance for dense SNP and resequencing data. *Genetic Epidemiology*, *32*, 179–185.

Huang, L., Li, Y., Singleton, A. B., Hardy, J. A., Abecasis, G., Rosenberg, N. A., & Scheet, P. (2009). Genotype-imputation accuracy across worldwide human populations. *American Journal of Human Genetics*, *84*, 235–250.

Hyytinen, A., & Ilmakunnas, P. (2007). What distinguishes a serial entrepreneur? *Industrial and Corporate Change*, *16*, 793–821.

International Schizophrenia Consortium, Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., ..., Scolnick, E. M. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature, 460*, 748-52.

Ioannidis, J. P. A. (2005). Why most published research findings are false. *PLOS Medicine*, *2*(8), e124.

Ioannidis, J. P. A. (2008). Why most discovered true associations are inflated. *Epidemiology, 19*, 640-648.

Jamal, M. (1997). Job stress, satisfaction, and mental health: An empirical examination of selfemployed and non-self-employed Canadians. *Journal of Small Business Management, 35*, 48–57.

Jang, K. L., Livesley, W. J., & Vemon, P. A. (1996). Heritability of the big five personality dimensions and their facets: a twin study. *Journal of Personality, 64*, 577–592.

Jencks, C. (1980). Heredity, environment, and public policy reconsidered. *American Sociological Review, 45*, 723–736.

Johnson, A. M, Vernon, P. A., & Feiler, R. A. (2008). Behavioral genetic studies of personality: an introduction and review of the results of 50+ years of research. In: G. Boyle, D.H. Saklofske, & G. Matthews, *Handbook of personality theory and assessment* (pp. 145-173). London: Sage.

Johnson, W., Bouchard, T. J., Krueger, R. F., McGue, M., & Gottesman, I. I. (2004). Just one g: consistent results from three test batteries. *Intelligence, 32*, 95–107.

Juster, T. F., & Suzman, R. (1995). An overview of the Health and Retirement Study. *Journal of Human Resources, 20*, 7-56.

Kahneman, D., & Deaton, A. (2010). High income improves evaluation of life but not emotional well-being. *Proceedings of the National Academy of Sciences of the United States of America, 107*, 16489–16493.

Kahneman, D., & Krueger, A. B. (2006). Developments in the measurement of subjective well-being. *Journal of Economic Perspectives, 20*, 3–24.

Kang, H. M., Sul, J. H., Service, S. K., Zaitlen, N. A., Kong, S. Y., Freimer, N. B., … Eskin, E. (2010). Variance component model to account for sample structure in genome-wide association studies. *Nature Genetics, 42*, 348–354.

Karasek, R. A. (1979). Job demands, job decision latitude, and mental strain: Implications for job redesign. *Administrative Science Quarterly, 24*, 285–308.

Karasek, R. A., & Theorell, T. (1990). *Healthy work: Stress, productivity, and the reconstruction of working life*. New York, NY, USA: Basic Books.

Keller, M. C. (2014). Gene × environment interaction studies have not properly controlled for potential confounders: the problem and the (simple) solution. *Biological Psychiatry, 75*, 18-24.

Kempthorne, O. (1997). Heritability: Uses and abuses. *Genetica, 99*, 109–112.

Kirzner, I. M. (1973). *Competition and entrepreneurship*. Chicago, IL, USA: The University of Chicago Press.

Klapper, L., Amit, R., Guillen, M. F., & Quesada, J. M. (2007). *Entrepreneurship and firm formation across countries.* (World Bank Policy Research Working Paper 4313). Available from http://d1c25a6gwz7q5e.cloudfront.net/papers/1345.pdf.

Koellinger, P. D., & Thurik, A. R. (2012). Entrepreneurship and the business cycle. *Review of Economics and Statistics*, *94*, 1143–1156.

Koellinger, P. D., Van der Loos, M. J. H. M., Groenen, P. J. F., Thurik, A. R., Rivadeneira, F., Van Rooij, F. J. A., … Hofman, A. (2010). Genome-wide association studies in economics and entrepreneurship research: Promises and limitations. *Small Business Economics*, *35*, 1–18.

Koellinger, P. D., Van der Loos, M. J. H. M., Rietveld, C. A., Benjamin, D. J., Cesarini, D., Eklund, N., … Thurik, A. R. (2013). *The quest for "entrepreneurial genes" continues.* Manuscript submitted for publication.

Kristof-Brown, A. L., Zimmerman, R. D., & Johnson, E.C. (2005). Consequences of individuals' fit at work: A meta-analysis of person–job, person–organization, person–group, and person–supervisor fit. *Personnel Psychology*, *58*, 281-342.

Lager, A. C. J., & Torssander, J. (2012). Causal effect of education on mortality in a quasi-experiment on 1.2 million Swedes. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 8461–8466.

Lambert, J. C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., ... Amouyel, P. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics*, *45*, 1–9.

Lander, E. S. (2011). Initial impact of the sequencing of the human genome. *Nature*, *470*, 187–197.

Lander, E. S., & Schork, N. J. (1994). Genetic dissection of complex traits. *Science*, *265*, 2037–2048.

Lango Allen, H., Estrada, K., Lettre, G., Berndt, S. I., Weedon, M. N., Rivadeneira, F., … Hirschhorn, J. N. (2010). Hundreds of variants clustered in genomic loci and biological pathways affect human height. *Nature*, *467*, 832–838.

Lee, S. H., Decandia, T. R., Ripke, S., Yang, J., Sullivan, P. F., Goddard, M. E., … Wray, N. R. (2012). Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. *Nature Genetics*, *44*, 247–250.

Lee, S. H., Wray, N. R., Goddard, M. E., & Visscher, P. M. (2011). Estimating missing heritability for disease from genome-wide association studies. *American Journal of Human Genetics*, *88*, 294–305.

Lewin-Epstein, N., & Yuchtman-Yaar, E. (1991). Health risks of self-employment. *Work and Occupations*, *18*, 291–312.

Liang, K. Y., & Zeger, S. L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika*, *73*, 13–22.

Lichtenstein, P. Sullivan, P. F., Cnattingius, S., Gatz, M., Johansson, S., Carlström, E., … Pedersen, N. L. (2006). The Swedish Twin Registry in the third millennium: An update. *Twin Research and Human Genetics*, *9*, 875–882.

Liu, J. Z., Mcrae, A. F., Nyholt, D. R., Medland, S. E., Wray, N. R., Brown, K. M., … Macgregor, S. (2010). A versatile gene-based test for genome-wide association studies. *American Journal of Human Genetics*, *87*, 139–145.

Lleras-Muney, A. (2005). The relationship between education and adult mortality in the United States. *Review of Economic Studies*, *72*, 189-221.

Logan, J. (2009). Dyslectic entrepreneurs: The incidence; their coping strategies and their business skills. *Dyslexia*, *15*, 328-346.

Lubke, G. H., Hottenga, J. J., Walters, R., Laurin, C., De Geus, E. J., Willemsen, G., ... Boomsma, D. I. (2012). Estimating the genetic variance of major depressive disorder due to all single nucleotide polymorphisms. *Biological Psychiatry*, 72, 707–709.

Lykken, D. T., & Tellegen, A. (1996). Happiness is a stochastic phenomenon. *Psychological Science*, *7*, 186–189.

Lykken, D. T. (1982). Presidential address. Research with twins: The concept of emergenesis. *Psychophysiology*, *19*, 361–373.

Marchini, J., Howie, B., Myers, S., McVean, G., & Donnelly, P. (2007). A new multipoint method for genome-wide association studies by imputation of genotypes. *Nature Genetics*, *39*, 906–913.

Marioni, R. E., Davies, G., Hayward, C., Liewald, D., Kerrd, S. M., Campbell, A., ... Deary, I. J. (2014). Molecular genetic contributions to socioeconomic status and intelligence. *Intelligence*, *44*, 26–32.

Marshall, A. (1961). *Principles of Economics* (9th ed.). London, UK: Macmillan.

Martin, N. W., Medland, S. E., Verweij, K. J. H., Lee, S. H., Nyholt, D. R., Madden, P. A., … Martin, N. G. (2011). Educational attainment: A genome wide association study in 9538 Australians. *PLOS ONE*, *6*, e20128.

McCarthy, M. I., Abecasis, G. R., Cardon, L. R., Goldstein, D. B., Little, J., Ioannidis, J. P. A., & Hirschhorn, J. N. (2008). Genome-wide association studies for complex traits: Consensus, uncertainty and challenges. *Nature Reviews Genetics*, *9*, 356–369.

McGrath, R. G., & MacMillan, I. C. (2000). *The entrepreneurial mindset*. Boston, MA, USA: Harvard Business School Press.

National Center for Biotechnology Information. (2014). *dbSNP*. Retrieved from http://www.ncbi.nlm.nih.gov/SNP/snp_summary.cgi

National Center for Biotechnology Information. (2013). *ABHD5 abhydrolase domain containing 5*. Retrieved from http://www.ncbi.nlm.nih.gov/gene/51099

Nes, R. B., Røysamb, E., Tambs, K., Harris, J. R., & Reichborn-Kjennerud, T. (2006). Subjective well-being: genetic and environmental contributions to stability and change. *Psychological Medicine, 6*, 1033–1042.

Newland, G.A. (1981). Differences between left- and right-handers on a measure of creativity. *Perceptual and Motor Skills, 53*, 787-792.

Nicolaou, N., & Shane, S. (2009). Can genetic factors influence the likelihood of engaging in entrepreneurial activity? *Journal of Business Venturing, 24*, 1–22.

Nicolaou, N., & Shane, S. (2010). Entrepreneurship and occupational choice: Genetic and environmental influences. *Journal of Economic Behavior & Organization, 76*, 3–14.

Nicolaou, N., Shane, S., Adi, G., Mangino, M., & Harris, J. (2011). A polymorphism associated with entrepreneurship: Evidence from dopamine receptor candidate genes. *Small Business Economics, 36*, 151–155.

Nicolaou, N., Shane, S., Cherkas, L., Hunkin, J., & Spector, T. D. (2008a). Is the tendency to engage in entrepreneurship genetic? *Management Science, 54*, 167–179.

Nicolaou, N., Shane, S., Cherkas, L., & Spector, T. D. (2008b). The influence of sensation seeking in the heritability of entrepreneurship. *Strategic Entrepreneurship Journal, 2*, 7–21.

Nicolaou, N., Shane, S., Cherkas, L., & Spector, T. D. (2009). Opportunity recognition and the tendency to be an entrepreneur: A bivariate genetics perspective. *Organizational Behavior and Human Decision Processes, 110*, 108–117.

Papadatou-Pastou, M., Martin, M. Munafò, M. R., & Jones, G. V. (2008). Sex differences in left-handedness: A meta-analysis of 144 studies. *Psychological Bulletin, 134*, 677-699.

Parker, S. C. (2009). *The economics of entrepreneurship*. Cambridge, UK: Cambridge University Press.

Parslow, R. A., Jorm, A. F., Christensen, H., Rogers, B., Strazdins, L., & D'Souza, R. M. (2004). The association between work stress and mental health: A comparison of organizationally employed and self-employed individuals. *Work and Stress, 18*, 231-244.

Payton, A. (2009). The impact of genetic research on our understanding of normal cognitive ageing: 1995 to 2009. *Neuropsychology Review, 19*, 451–477.

Pearson, T. A., & Manolio, T. A. (2008). How to interpret a genome-wide association study. *Journal of the American Medical Association, 299*, 1335–1344.

Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2008). *Behavioral genetics* (5th ed.). New York, NY: Worth Publishers.

Plomin, R., DeFries, J., Knopik, V., & Neiderhiser, J. (2013). *Behavioral genetics* (6th ed.). New York, NY: Worth Publishers.

Price, A. L., Helgason, A., Palsson, S., Stefansson, H., St Clair, D., Andreassen, O. A., … Stefansson, K. (2009). The impact of divergence time on the nature of population structure: an example from Iceland. *PLOS Genetics, 5*, e1000505.

Price, A. L., Patterson, N. J., Plenge, R. M., Weinblatt, M. E., Shadick, N. A., & Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics, 38*, 904–909.

Prottas, D. J., & Thompson, C. A. (2006). Stress, satisfaction, and the work–family interface: A comparison of self-employed business owners, independents, and organizational employees. *Journal of Occupational Health Psychology, 11*, 366–378.

Psacharopoulos, G. (1985). Returns to education: A further international update and implications. *Journal of Human Resources, 20*, 583-604.

Purcell, S.M., Cherny, S. S., & Sham, P. C. (2003). Genetic power calculator: Design of linkage and association genetic mapping studies of complex traits. *Bioinformatics, 19*, 149–150.

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

Quaye, L., Nicolaou, N., Shane, S., & Mangino, M. (2012). A discovery genome-wide association study of entrepreneurship. *International Journal of Developmental Science, 6*, 127–135.

Ramsköld, D., Wang, E. T., Burge, C. B., & Sandberg, R. (2009). An abundance of ubiquitously expressed genes revealed by tissue transcriptome sequence data. *PLOS Computational Biology, 5*(12), e1000598.

Ravesteijn, B., Van Kippersluis, H., & Van Doorslaer, E. (2013). The contribution of occupation to health inequality. In: P.R. Dias , & O. O'Donnell (Eds.), *Research on Economic Inequality, Volume 21: Health and Inequality* (pp. 311-332). Bingley, UK: Emerald Group Publishing Limited.

Ree, M. J. & Earles, J. A. (1991). The stability of g across different methods of estimation. *Intelligence, 15*, 271–278.

Rietveld, C. A. (2013). *Heritability and the Covenant.* Manuscript submitted for publication.

Rietveld, C. A., Cesarini, D., Benjamin D. J., Koellinger, P. D., De Neve, J. E., Tiemeier H, ... Bartels, M. (2013a). Molecular genetics and subjective well-being. *Proceedings of the National Academy of Sciences of the United States of America, 110*, 9692-9697.

Rietveld, C. A., Conley, D., Eriksson, N., Esko, T., Medland, S. E., Vinkhuyzen, A. A. E., … Social Science Genetic Association Consortium. (2014a). Replicability and robustness of GWAS for behavioral traits. *Psychological Science, in press*.

Rietveld, C. A., Esko, T., Davies, G., Pers, T. H., Benyamin, B., Chabris, C. F., … Social Science Genetic Association Consortium. (2014b). *Proxy-phenotype method edentifies common genetic variants associated with cognitive performance.* Manuscript submitted for publication.

Rietveld, C. A., Groenen, P. J. F., Koellinger, P. D., Van der Loos, M. J. H. M., & Thurik, A. R. (2013b). *Living forever: entrepreneurial overconfidence at older ages.* (ERIM Report Series in Management ERS-2013-012-STR). Rotterdam, The Netherlands: Erasmus Research Institute of Management.

Rietveld, C. A., Hessels, J., & Van der Zwan, P. W. (2014). *Unhealthy perceptions about entrepreneurship*. Manuscript submitted for publication.

Rietveld, C. A., Medland, S. E., Derringer, J., Yang, J., Esko, T., Martin, N. W., … Koellinger, P. D. (2013c). GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. *Science, 340*, 1467-1471.

Rietveld, C. A., & Okbay, A. (2014). On improving the credibility of candidate gene studies: A review of candidate gene studies published in Emotion. Manuscript submitted for publication.

Rietveld, C. A, & Van Burg, E. (2014). Religious beliefs and entrepreneurship among Dutch protestants. *International Journal of Entrepreneurship and Small Business, in press.*

Rietveld, C. A., Van Kippersluis, H., & Thurik, A. R. (2014). Self-employment and health: Barriers or benefits? *Health Economics, in press*.

Robins, J. M., & Greenland, S. (1992). Identifiability and exchangeability for direct and indirect effects. *Epidemiology, 3*, 143-155.

Roff, D., & Bentzen, P. (1989). The statistical analysis of mitochondrial DNA polymorphisms: chi 2 and the problem of small samples. *Molecular Biology and Evolution, 6*, 539-545.

Røysamb, E., Harris, J. R., Magnus, P., Vitterso, J., & Tambs, K. (2002). Subjective well-being. Sex-specific effects of genetic and environmental factors. *Personality and Individual Differences, 32*, 211–223.

Ruebeck, C. S., Harrington, J. E., & Moffitt, R. (2007). Handedness and earnings. *Laterality: Asymmetries of Body, Brain and Cognition, 12*, 101-120.

Scherpenzeel, A. (2011). Data collection in a probability-based internet panel: How the LISS panel was built and how it can be used. *Bulletin of Sociological Methodology. 109*, 56-61.

Seligman, M. E. P., & Csikszentmihalyi, M. (2000). Positive psychology: An introduction. *American Psychologist, 55*, 5–14.

Shaffer, J. P. (1995). Multiple hypothesis testing. *Annual Review of Psychology*, *46*, 561–584.

Shane, S. (2010). *Born entrepreneurs, born leaders: How your genes affect your work life.* New York, NY: Oxford University Press.

Shane, S., & Nicolaou, N. (2013). The genetics of entrepreneurial performance. *International Small Business Journal*, *31*, 473-495.

Shane, S., Nicolaou, N., Cherkas, L., & Spector, T. D. (2010). Genetics, the Big Five, and the tendency to be self-employed. *Journal of Applied Psychology*, *95*, 1154–1162.

Shane, S., & Venkataraman, S. (2000). The promise of entrepreneurship as a field of research. *Academy of Management Review*, *25*, 217–226.

Shyn, S. I., Shi, J., Kraft, J. B., Potash, J. B., Knowles, J. A., Weissman, M. M., … Hamilton, S. P. (2011). Novel loci for major depression identified by genome-wide association study of sequenced treatment alternatives to relieve depression and meta-analysis of three studies. *Molecular Psychiatry*, *16*, 202–215.

Silventoinen, K. (2003a). Determinants of variation in adult body height. *Journal of Biosocial Science*, *35*, 263–285.

Silventoinen, K., Sammalisto, S., Perola, M., Boomsma, D. I., Cornes, B. K., Davis, C., ... Kaprio, J. (2003b). Heritability of adult body height: A comparative study of twin cohorts in eight countries. *Twin Research*, *6*, 399–408.

Smith, A. (1937). *An inquiry into the nature and causes of the wealth of nations*. New York, NY: Random House.

Smith, G. D., & Ebrahim, S. (2003). 'Mendelian randomization': Can genetic epidemiology contribute to understanding environmental determinants of disease?. *International Journal of Epidemiology*, *32*, 1-22.

Speliotes, E. K., Willer, C. J., Berndt, S. I., Monda, K. L., Thorleifsson, G., Jackson, A. U., … Loos, R. J. F. (2010). Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nature Genetics*, *42*, 937–948.

Steinthorsdottir, V., Thorleifsson, G., Reynisdottir, I., Benediktsson, R., Jonsdottir, T., Walters, G. B., … Stefansson, K. (2007). A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. *Nature Genetics*, *39*, 770–775.

Stefansson, H., Meyer-Lindenberg, A., Steinberg, S., Magnusdottir, B., Morgen, K., Arnarsdottir, S., ... Stefansson, K. (2014). CNVs conferring risk of autism or schizophrenia affect cognition in controls. *Nature*, *505*, 361-366.

Stephan, U., & Roesler, U. (2010). Comparison of entrepreneurs' and employee's health in a national representative sample. *Journal of Occupational and Organizational Psychology*, *83*, 717-738.

Stowasser, T., Heiss, F., McFadden, D., & Winter, J. (2011). *Healthy, wealthy and wise? revisited: An analysis of the causal pathways from socio-economic status to health.* (National Bureau of Economic Research Working Paper 17273). Available from: http://www.nber.org/papers/w17273.

Stubbe, J. H., Posthuma, D., Boomsma, D. I., & De Geus, E.J.C. (2005). Heritability of life satisfaction in adults: A twin-family study. *Psychological Medicine*, *35*, 1581–1588.

Taubman, P. (1976). The determinants of earnings: Genetics, family, and other environments: A study of white male twins. *American Economic Review*, *66*, 858–870.

Taylor, M. P. (1999). Survival of the fittest? An analysis of self-employment duration in Britain. *The Economic Journal*, *109*, 140-155.

Taylor, A. E., Davies, N. M., Ware, J. J., VanderWeele, T., Smith, G. D., & Munafò, M. R. (2014). Mendelian randomization in health research: Using appropriate genetic variants and avoiding biased estimates. *Economics & Human Biology*, *13*, 99-106.

Tellegen, A., Lykken, D. T., Bouchard, T. J., Wilcox, K. J., Segal, N. L., & Rich, S. (1988). Personality similarity in twins reared apart and together. *Journal of Personality and Social Psychology*, *54*, 1031–1039.

Terracciano, A., Sanna, S., Uda, M., Deiana, B., Usala, G., Busonero, F., … Costa, P. T., Jr. (2010). Genome-wide association scan for five major dimensions of personality. *Molecular Psychiatry*, *15*, 647–656.

Tetrick, L. E., Slack. K., Da Silva, N., & Sinclair, R. R. (2000). A comparison of the stress-strain process for business owners and nonowners: Differences in job demands, emotional exhaustion, satisfaction, and social support. *Journal of Occupational Health Psychology*, *5*, 464–476.

The 1000 Genomes Project Consortium. (2010). A map of human genome variation from population-scale sequencing. *Nature*, *467*, 1061–1073.

Theorell, T., & Karasek, R. A. (1996). Current issues relating to psychosocial job strain and cardiovascular disease research. *Journal of Occupational Health Psychology*, *1*, 9–26.

The International HapMap Consortium. (2005). A haplotype map of the human genome. *Nature*, *437*, 1299–1320.

Torres, O. (2012). *La santé du dirigeant: De la souffrance patronage à l'entrepreneuriat salutaire*. Brussels, Belgium: De Boeck.

Turkheimer, E. (2012). Genome wide association studies of behavior are social science. In: K. S. Plaisance & T. A. C. Reydon (Eds), Philosophy of behavioral biology (pp. 43–64). New York: Springer.

United Nations Educational, Scientific and Cultural Organization. (2006). *International Standard Classification of Education 1997: ISCED 1997. May 2006 Re-edition*. Available from http://www.uis.unesco.org/Library/Documents/isced97-en.pdf

Vaillant, G. E. (2012). Positive mental health: is there a cross-cultural definition? *World Psychiatry*, *11*, 93–99.

Van der Gaast, J. P., Rietveld, C. A., Gabor, A. F. , & Zhang, Y. (2011). A Tabu Search algorithm for application placement in computer clustering. *Computers & Operations Research*, *59*, 38-46.

Van der Loos, M. J. H. M. (2013). *Molecular genetics and hormones: New frontiers in entrepreneurship research*. Rotterdam, The Netherlands: Erasmus Research Institute of Management.

Van der Loos, M. J. H. M., Haring, R., Rietveld, C. A., Baumeister, S. E., Groenen, P. J. F., Hofman, A., … Thurik, A. R. (2013a). Measures of bioactive serum testosterone are not associated with entrepreneurial behavior in two independent observational studies. *Physiology & Behavior, 119*, 110–114.

Van der Loos, M. J. H. M., Koellinger, P. D., Groenen, P. J. F., Rietveld, C. A., Rivadeneira, F., Van Rooij, F. J. A., … Thurik, A. R. (2011). Candidate gene studies and the quest for the entrepreneurial gene. *Small Business Economics*, *37*, 269–275.

Van der Loos, M. J. H. M., Koellinger, P. D., Groenen, P. J. F., & Thurik, A. R. (2010). Genome-wide association studies and the genetics of entrepreneurship. *European Journal of Epidemiology*, *25*, 1–3.

Van der Loos, M. J. H. M., Rietveld, C. A., Eklund, N., Koellinger, P. D., Rivadeneira, F., Abecasis, G. R., … Thurik, A. R. (2013b). The molecular genetic architecture of self-employment, *PLOS ONE*, *8*, e60542.

Van Praag, C. M., & Van Ophem, H. (1995). Determinants of willingness and opportunity to start as an entrepreneur. *Kyklos*, *48*, 513-540.

Verheul, I., Thurik, A. R., Hessels, J., & Van der Zwan, P. W. (2010). *Factors influencing the entrepreneurial engagement of opportunity and necessity entrepreneurs.* (Panteia/EIM Research Report H2010/11). Available from: http://ideas.repec.org/p/eim/papers/h201011.html.

Verweij, K. J. H., Yang, J., Lahti, J., Veijola, J., Hintsanen, M., Pulkki-Råback, L., … Zietsch, B. P. (2012). Maintenance of genetic variation in human personality: Testing evolutionary models by estimating heritability due to common causal variants and investigating the effect of distant inbreeding. *Evolution*, *66*, 3238–3251.

Verweij, K. J. H., Zietsch, B. P., Medland, S. E., Gordon, S. D., Benyamin, B., Nyholt, D. R., … Wray, N. R. (2010). Genome-wide association study of Cloninger's temperament scales: Implications for the evolutionary genetics of personality. *Biological Psychology*, *85*, 306–317.

Vinkhuyzen, A. A. E., Pedersen, N. L., Yang, J., Lee, S. H., Magnusson, P. K. E., Iacono, W. G., … Wray, N. R. (2012). Common SNPs explain some of the variation in the personality dimensions of neuroticism and extraversion. *Translational Psychiatry*, *2*, e102.

Visscher, P. M., Brown, M. A., McCarthy, M. I., & Yang, J. (2012a). Five years of GWAS discovery. *American Journal of Human Genetics*, *90*, 7–24.

Visscher, P. M., Goddard, M. E., Derks, E. M., & Wray, N. R. (2012b). Evidence-based psychiatric genetics, AKA the false dichotomy between common and rare variant hypotheses. *Molecular Psychiatry*, *17*, 474–485.

Wainwright, M. A., Wright, M. J., Geffen, G. M., Luciano, M., & Martin, N. G. (2005). The genetic basis of academic achievement on the Queensland Core Skills Test and its shared genetic variance with IQ. *Behavior Genetics*, *35*, 133–145.

Ward, T. B. (2004). Cognition, creativity, and entrepreneurship. *Journal of Business Venturing*, *19*, 173-188.

Ward, M. E., McMahon, G., St Pourcain, B., Evans, D. M., Rietveld, C. A., Benjamin, D. J., ... Timpson, N. J. (2014). Genetic variation associated with differential educational attainment in adults has anticipated associations with school performance in children. *PLOS ONE*, *9*, e100248.

Wernerfelt, N. C., Rand, D. G., Dreber, A., Montgomery, C. A., & Malhotra, D. (2012). *Arginine vasopressin 1a receptor (AVPR1a) RS3 repeat polymorphism associated with entrepreneurship.* (SSRN Discussion Paper No. 2141598). Retrieved from http://dx.doi.org/10.2139/ssrn.2141598.

Westhead, P., Ucbasaran, D., Wright, M., & Binks, M. (2005). Novice, serial and portfolio entrepreneur behavior and contributions. *Small Business Economics*, *25*, 109–132.

Willer, C. J., Li, Y., & Abecasis, G. R. (2010). METAL: Fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*, *26*, 2190–2191.

Wisdom, N. M., Callahan, J. L., & Hawkins, K.A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiology of Aging*, *32*, 63–74.

Wray, N. R., Purcell, S. M., & Visscher, P. M. (2011). Synthetic associations created by rare variants do not explain most GWAS results. *PLOS Biology*, *9*(1), e1000579.

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

Yang, J., Ferreira, T., Morris, A. P., Medland, S. E., Madden, P. A. F., Heath, A. C., … Visscher, P. M. (2012). Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nature Genetics*, *44*, 369–375.

Yang, J., Lee, S. H., Goddard, M. E., & Visscher, P. M. (2011a). GCTA: A tool for genome-wide complex trait analysis. *American Journal of Human Genetics*, *88*, 76–82.

Yang, J., Weedon, M.N., Purcell, S., Lettre, G., Estrada, K., Willer, C.J., ... GIANT Consortium (2011b). Genomic inflation factors under polygenic inheritance. *European Journal of Human Genetics*, *19*, 807-812.

Yoon, J., & Bernell, S.L. (2013). The effect of self-employment on health, access to care, and health behavior. *Health*, *5*, 2116-2127.

Zhang, Z., Zyphur, M. J., Narayanan, J., Arvey, R. D., Chaturvedi, S., Avolio, B. J., … Larssong, G. (2009). The genetic basis of entrepreneurship: Effects of gender and personality. *Organizational Behavior and Human Decision Processes*, *110*, 93–107.

Ziegler, A., & König, I. R. (2010). *A statistical approach to genetic epidemiology* (2nd ed.). Weinheim: Wiley-VCH Verlag GmbH , & Co. KGaA.

Zissimopoulos, J., & Karoly, L. A. (2007). Transitions to self-employment at older ages: The role of wealth, health, health insurance, and other factors. *Labour Economics*, *14*, 269-295.

Zuk, O., Hechter, E., Sunyaev, S. R., & Lander, E. S. (2012). The mystery of missing heritability: Genetic interactions create phantom heritability. *Proceedings of the National Academy of Sciences of the United States of America*, *109*, 1193–1198.

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ESSAYS ON THE INTERSECTION OF ECONOMICS AND BIOLOGY

Biological economics is the interdisciplinary research field in which the interaction between human biology and economics is investigated, and human beings are primarily seen as biological organisms. This thesis adopts a perspective in which individual economic choices and outcomes are connected to individual biological characteristics

The value of research on the intersection of economics and biology is at least threefold. First, knowledge about biological predispositions to economic choices and outcomes improves our understanding of the causes and consequences of individual differences. Second, biological measures known to be associated with economic choices and outcomes could be used in (otherwise non-biological) empirical work as control variables or instrumental variables. Third, information about economic predisposition to biological states and outcomes may result in targeted interventions to prevent undesired outcomes.

Although it has been known for some time that many economic choices and outcomes are heritable, no robust, replicable genetic predisposition to these choices and outcomes have been found. This thesis shows that it is possible to find such associations in a robust and replicable manner, by applying relatively crude methods in combination with statistical rigor. This thesis also presents evidence that self-employed individuals are generally healthier than wage workers and that the selection of comparatively healthier individuals into self-employment accounts for the positive cross-sectional association. It presents tentative evidence that, if anything, engaging in self-employment is bad for one's health. In addition, the anecdotes that entrepreneurship is a particularly good occupation for dyslectic and left-handed individuals could not be substantiated.

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