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Abstract

Purpose. This study explores the social, biological, and genetic determinants of depression in later life. It adds complexity to the idea that later life depression is a natural outgrowth of vascular impairment, antagonistic pleiotropy, or compromised neuroanatomical structures. **Approach.** The study uses the NAS-NRC Twin Registry of World War II Veterans. The use of twins allows for the exploration of gene-environment interplay. A recent survey instrument associated with the registry contains numerous indicators of health, as well as an established measure of geriatric depression. **Findings.** The results show that education has a strong negative relationship with depression among those in their 70s and early 80s. Although this relationship is partly explained by lower rates of cardiovascular disease and diabetes among the well-educated, the relationship between education and many common physical illnesses is quite small. Most people of this age experience at least one chronic illness. The relationship between education and depression is explained, instead, by reduced impairments in activities of daily living. These impairments are not an inevitable outgrowth of declining health. The well-educated are better able to moderate the impact of poor health on daily functioning. Moreover, the well educated are able to avoid the otherwise strong genetic risks for depression in later life. Gene \times environment models show a high heritability for later life depression on average, but also reveal that this heritability declines with increasing education. Among those with a four-year college degree, the heritability of depression is very small. **Value.** These patterns are interpreted in light of models for understanding compensatory gene \times environment interactions. These models emphasize the importance of especially enriched environments for overcoming genetic risk.

Keywords

Aging, Aged, Later Life, Biology of Aging, Depression, Genetic, Social, Biological, Heritability, Educational Attainment, NAS-NRC Twin Registry of World War II Veterans, Socioeconomic Status, Disease

Disciplines

Biological and Physical Anthropology | Demography, Population, and Ecology | Family, Life Course, and Society | Geriatrics | Mental and Social Health | Psychology | Social and Behavioral Sciences | Sociology

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Natural Symptoms?

The Intersection of Social, Biological, and Genetic Determinants of Depression in Later Life

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Abstract

Purpose. This study explores the social, biological, and genetic determinants of depression in later life. It adds complexity to the idea that later life depression is a natural outgrowth of vascular impairment, antagonistic pleiotropy, or compromised neuroanatomical structures.

Approach. The study uses the NAS-NRC Twin Registry of World War II Veterans. The use of twins allows for the exploration of gene-environment interplay. A recent survey instrument associated with the registry contains numerous indicators of health, as well as an established measure of geriatric depression.

Findings. The results show that education has a strong negative relationship with depression among those in their 70s and early 80s. Although this relationship is partly explained by lower rates of cardiovascular disease and diabetes among the well-educated, the relationship between education and many common physical illnesses is quite small. Most people of this age experience at least one chronic illness. The relationship between education and depression is explained, instead, by reduced impairments in activities of daily living. These impairments are not an inevitable outgrowth of declining health. The well-educated are better able to moderate the impact of poor health on daily functioning. Moreover, the well-educated are able to avoid the otherwise strong genetic risks for depression in later life. Gene \times environment models show a high heritability for later life depression on average, but also reveal that this heritability declines with increasing education. Among those with a four-year college degree, the heritability of depression is very small.

Value. These patterns are interpreted in light of models for understanding compensatory gene \times environment interactions. These models emphasize the importance of especially enriched environments for overcoming genetic risk.

Depression in later life presents unique challenges. For one, its clinical characteristics are different from depression presented earlier in the life course. For many older adults, their experience with depression is their first experience with the disorder, even though the median age-of-onset for major depression is quite young (Bruce et al. 2002). Relative to depression presented earlier, later life depression also tends to assume a more somatic and less affective character, leading some to characterize it as "depression without sadness" (Gallo, Rabins, and Lyketsos 1997). In addition, later life depression often assumes a milder form. Although major depressive *disorder* is less common in later life than in middle age, clinically significant depressive *symptoms* are more common (Blazer 2003). For all these reasons, depression in later life often eludes detection, but it can nonetheless have a significant impact on the lives of older people, including exacerbating the consequences of physical illness (Romanelli, Fauerbach, Bush, and Ziegelstein 2002).

Later life depression also presents a challenge for social scientists. Conventional sociological models of depression emphasize environmental influences and forestalled illness. Although there is broad agreement that environmental influences are important in later life, too, the literature on later life depression has a more biological and endemic character. There are good reasons for this. The relationship between socioeconomic status and health tends to decline with age, reflecting a more general decline in the strength of the relationship between social risk factors and health (House, Kessler, and Herzog 1990). The same has been found for depression (George 1992). The explanation for depression in later life lies elsewhere. Many psychobiological changes associated with aging and are also correlated with depression (Blazer 2002). Several studies show, for instance, that depression over the age of 70 is largely a function of declining physical health and neurological impairment. Indeed, the influence of declining health is sufficiently powerful to overwhelm

the many positive psychological improvements ordinarily associated with maturity (Mirowsky and Ross 1992). The potent relationship between poor health and depression reflects its multidimensionality: deteriorating health implies biological dysfunction, impairments in activities of daily living, and a diminished sense of control, all of which are independently related to depression but combine perniciously in later life (Rodin 1986).

With these observations in mind, depression can appear a pervasive and even natural feature of aging. Consistent with this intuition, recent research has moved in a more biological and systematic direction, highlighting physiological substrates common to declining physical, cognitive, and mental health. Some research in this vein has focused on structural changes to the brain. By the same token, research has posited a depression-executive dysfunction syndrome, linking assorted vascular risk factors to later life depression and cognitive impairment (Alexopoulos 2005). Similarly, some argue for the growing importance of genetic influences with age, premised on the idea that late-acting and harmful genetic influences cannot be selected out of the population and harm functioning in later life. By this logic, the contributions of genes to depression may be even greater in later life than earlier in the life course (McGue and Johnson 2008).

In this study, I use these challenges as an opportunity. I explore the relationship between education and depression in later life. Of the assorted fundamental causes of health, education remains perhaps the most important. I explore the relationship between education and depression in two ways. First, I attempt to explain the relationship with assorted biological characteristics implicated in later life depression. Second, I explore whether the consequences of poor health matter more than poor health *per se*, exploring impairments in activities of daily living. Third, I explore gene \times environment interactions, in particular whether education moderates the impact of genetic influences on depression. I do

so using a large cohort sample of male twins, which permits an analysis of gene × environment interplay. Across these investigations I attempt to develop a biosocial perspective that better balances the biology of aging with the enduring resources of social position. Despite acknowledging the complex web of internal and external factors that affect depression in later life (Blazer 2002, esp. pp. 26-27), research still tends to routinely focus on one type of influence at a time, thereby creating some unfortunate silos.

Background

The literature of depression in later life focuses on the connection between mental and physical health. Indeed, in perhaps no other time in life is the connection as strong. Physical functioning tends to remain stable through the adult years, but begins to decline at an accelerating rate sometime after the age of 70 (Mirowsky and Ross 1992). These declines cut across systems and activities, applying to vigorous physical activities, most dimensions of cognitive performance, and basic activities of daily living. In turn, poor health has been linked to depression, mapping the growth in depressive symptoms with age to the acceleration of illness (Mirowsky and Ross 1992).

From these observations, research has developed a variety of mechanistic frameworks for understanding the connection between specific diseases and depression. In reference to the full range of chronic medical illnesses implicated in the connection, Alexopoulos (2005) refers to *depression executive dysfunction syndrome*. A number of specific diseases have been found to be especially important, including diabetes, hypertension, and cardiovascular disease (Hickie et al. 2001; Ranga and Krishnan 2002). Depression is common among those with vascular impairment, especially following a heart attack (Carney and Freedland 2003) or stroke (Park et al. 2007). Similarly, depression is elevated among those with diabetes (Li,

Mokdad, Ford, and Strine 2008). These diseases have been linked to depression through pathways related to dysfunction in neuroendocrine, sympathetic, or inflammatory systems (Krishnan et al. 2002). They have also been linked to depression through compromised neurocortical structures (Alexopoulos 2005), putting neurological health front-and-center as the most proximate explanation for later life depression (Ranga and Krishnan 2002). Most elderly patients with depression exhibit patchy deep white matter lesions, whereas most patients under the age of 45 with depression do not (Krishnan et al. 1988).

Yet the causes of later life depression should not be considered entirely in terms of disease and its neurological correlates. A recent review of later-life depression concludes that impairments in activities of daily living may also be an important common pathway in later life depression (Fiske, Wetherell, and Gatz 2009). This argument is not incompatible with biological causation, of course, but it suggests important intersections between the environment and biology and, by implication, the possibility of moderation even in the presence of illness. Insofar as the disability associated with illness is minimized, the effects of illness on depression might be minimized as well. In addition, some psychological changes associated with aging are offsetting of depression. For instance, there is evidence that psychological resilience increases with age (Mirowsky and Ross 1992), allowing individuals to cope better with, for example, economic hardship and other adversities common among older persons (Mirowsky and Ross 2001).

Still, the overall pattern is of increasing depressive symptoms with age. There is no escaping the implication that depression in later life may be bought on by some of the most prevalent diseases of aging. Nearly all older adults will experience some chronic illness. Even if the primary mechanism linking poor health to depression is impaired functioning rather than physiological or neurological dysfunction, the evidence is clear that functioning, too,

declines with age. At a psychological level, existential fears occasioned by deteriorating health are not uncommon (Blazer 2002). Even the strongest case for environmental influences in depression stops short of arguing that social causes are crucial to promoting health in later life, arguing instead that the best we can do is push back the onset of disease a few years, and that for this purpose investments earlier in life work better (House, Kessler, and Herzog 1990). Even the relationship between education and depression declines with age (George 1992). A review of recent genetic research further underscores the implication that depression in later life might be fundamentally a biological matter.

Genetic Influences in Late Life Depression

Two evolutionary models anticipate age-specific genetic influences underlying the assorted dimensions of biological aging (see McGue and Johnson 2008 for a review). The *mutation accumulation* model argues that post-reproductive deterioration occurs because of the buildup of harmful genetic mutations that are late-acting and unselected (Hamilton 1966), whereas the *antagonistic pleiotropy* model argues that mutations that confer an advantage early in life may be deleterious later on (Williams 1957). Although positing different mechanisms, both models anticipate that genetic influences are strong in later life and sometimes increase with age.

Studies seeking to identify genes related to later life depression find some overlap between the genes related to depression among younger persons as among older persons, although the overlap is generally weak (see Jansson et al. 2003 on the 5-HTT serotonin transporter gene). A number of studies have focused, instead, on genes related to other dimensions of physical health as indirect antecedents to later life depression. In this vein, polymorphisms related to vascular disease are more common among late-onset cases of depression than earlier-onset (Hickie et al. 2001) and, for this reason, one explanation for the

co-occurrence of illness and depression in later life is genetic factors common to both vascular lesions and depression. Similarly, research has found a strong genetic component to functional impairments (Gurland, Page, and Plassman 2004) and brain reserve (Finkel, Pedersen, McGue, and McClearn 1995), both of which are related to depression.

The implication of this research is that depression in later life may be strongly influenced by genes, either directly or indirectly through the many assorted neurobiological factors associated with depression. Summarizing the literature on successful aging, Depp, Vahia, and Jeste (2010) conclude that “genes and other ‘hardware’ provide parameters around individual age-related trajectories” (p. 538). Invoking a similar sense of limits, McGue and Christensen (1997) argue the heritability of later life depression is greater than is usually appreciated. Their own estimates of the heritability of depression among those 75 and older are around 34% and do not vary by whether the symptoms are somatic or affective. Twin studies of multiple indicators of successful aging and functioning find heritabilities that are only slightly lower than the heritability for longevity itself (Gurland, Page, and Plassman 2004). Consistent with a model of antagonistic pleiotropy, some evidence indicates that inflammation processes may be essential to good health earlier in life but lead to depression (and other illnesses) later on (Franceschi 2007).

Despite its overdetermined character, this research area also invites speculation about environmental factors that could moderate genetic risk. There is, for example, wide variation across study samples in the estimated heritability of later life depression, with some finding quite low heritability (Gatz, Pederson, Plomin, and Nesselroade 1992; Krishnan 1991), while others find moderate or high heritability (McGue and Christensen 1997). This variability perhaps implies variation in environments, a topic that has yet to be explored fully. In addition, there is evidence that education is protective for at least some of the factors

indirectly related to depression. For instance, education contributes to cognitive reserve and so might protect against depression that is occasioned by neurobiological loss (Fratiglioni, Paillard-Borg, and Winblad 2004). Insofar as there are interactions between education and genes, a compensatory interaction seems most likely (Shanahan and Hofer 2005).

Compensation refers to situations in which an especially enriched environment can neutralize genetic risks that otherwise prevail in the average environment. In this case, a high level of education might be sufficiently powerful in improving neurological health that it reduces the influence of genetic factors that normally increase the risk of depression.

Research Questions

I will ask three related sets of questions:

- 1). What is the relationship between education and depression in later life, and how does that relationship compare to that found between education and other illnesses?
- 2). What is the relationship between poor physical health and depression? Can the relationship between education and depression be explained by the absence of disease or is it better explained by reduced impairments in activities of daily living?
- 3). What is the heritability of depression in later life? Does education moderate this heritability?

Data

To answer these questions, I will use the National Academy of Sciences-National Research Council (NAS-NRC) Twin Registry of World War II Veterans (Page 2002). The registry is one of the oldest population-based twin registries in the US. The data have been used extensively in the discovery of genetic influences in smoking, suicide, Parkinson's disease, and

Alzheimer's disease, among other illnesses and behaviors (Page 2006). Descriptive clinical studies remain the focus of the registry and investigations of this sort are ongoing. The data have yet to be used extensively by social scientists, but this situation presents an opportunity: it allows me to show what happens when you situate the study of heritability in a more sociological context.

Initial planning and data collection began several decades ago. In 1955, the NAS-NRC began to identify twins born between 1917 and 1927 who had served in the armed forces during World War II. Given the size of the armed forces during the conflict, this effort led to the identification of a large number of twin siblings who had both served in the war. The initial population was 15,924 twin pairs or 31,848 individual twins. From this population, the registry followed the twins over time and collected survey data via mail questionnaire in 1967, 1983, and 2000. The number of twin-pair respondents for these surveys was 4,700, 3,600, and 2,060 respectively. Zygosity was determined through multiple methods: information regarding basic biometrics culled from military records; questionnaire data regarding physical similarity; fingerprints; and, for a select sample, more sophisticated blood testing (Jablon, Neel, Gershowitz, and Atkinson 1967). The concordance among these methods is high, although there were still a small number of twin-pairs (less than 6%) for whom zygosity could not be confidently established.

The NAS-NRC sample is unusual in five respects. First, the sample is limited to whites, although African Americans did serve in the war. This is a limitation of representation, especially given the environmental variation a more racially diverse sample would necessarily capture. However, the use of a single race reduces the possibility of population stratification, which is important for evaluating genetic influences. Second, the sample is exclusively men. This, too, limits the representation of data, but in this case in ways that are particularly

relevant to depression. Depression is half as common in men as women and may involve somewhat different etiologies. The genetic processes behind depression may operate differently between sexes (Kendler et al. 1993) and declining testosterone may play a role in depression among aging men (Seidman and Walsh 1999). Fourth, I use only the 2000 wave of survey data, which is the only wave containing a measure of depression. This limits the sample to those aged 70 to 82, although this age group is, of course, the focus of my interests. Fifth, the sample consists exclusively of veterans. Because members of the armed forces must pass a physical exam, veterans are, on average, healthier than their non-veteran age peers. Furthermore, veterans tend to have a higher level of educational attainment relative to nonveterans. Among World War II veterans, both military service itself and the educational benefits associated with the GI Bill increased college attainment (Bound and Turner 2002). For all these reasons, the conclusions drawn here may not overlap with those drawn from other racial/ethnic groups, from women, or from other age groups/cohorts. Nevertheless, the large sample permits considerable variation in my outcomes of interest, as well as variation in my key environmental measure, education. After dropping cases for which zygosity could not be established, incomplete twin pairs, or pairs for which there was insufficient item response to code depression, the resulting sample size was 3710 twins over 1855 pairs (because twin pairs are complete, the sample size for pairs is always half the sample size for individuals).

Measure of Depression

The symptoms of depression among older adults differ from those among younger adults (Christensen et al. 1999). Older adults are less likely to report affective symptoms and more likely to report a loss of interest, somatic symptoms, and cognitive deficits. For this reason, even the most well-established measures of depressive symptoms, like the CES-D, might not work well among older adults. I use the Geriatric Depression Scale (GDS), which

was designed to reflect the symptomatology of depression among older persons (Yesavage et al. 1983). Survey measures of depression conventionally include a disproportionate number of somatic symptoms, which accurately reflects depression as it is defined in formal nomenclature but compromises the ability of researchers to discriminate between different degrees of depression among older persons. The GDS includes a larger number of psychological and somatic symptoms, each with a plain interpretation for older adults and a simple yes/no response category. The 15-item version of the GDS performs well relative to standards (Lyness et al. 1997; Marc, Raue, and Bruce 2008). The items are listed in Appendix A. The scale was scored by summing the items (after recoding the positive items) and dividing by 15, thereby creating the mean response, ranging from zero to one. Although a simple sum is the conventional coding for the GDS, this alternative coding provides range symmetry with some of the other variables used in the study and can still be interpreted as the count of symptoms after multiplying by 15.

Other Variables

The single most important independent variable is education, measured for most models as the years of completed schooling, but broken down into relevant degree categories for some sensitivity analyses. All the models also control for marital status using a three-part division between married, widowed, and divorced/separated/never married (the reference category). Bereavement is among the most stressful life events among older adults. The three-part coding of marital status allows me to evaluate the relationship between widowhood and depression on its own, although without information on how recent the death of a spouse was. The models also control for age. Although over the entire life span the relationship between age and depressive symptoms is non-linear, over the age span examined here the relationship is linear.

The remaining covariates pertain to physical illness and health-related functioning. The models control for the set of conditions most commonly linked to depression, including hypertension, heart attack, stroke, diabetes, and activities of daily living. The four illnesses were assessed by asking respondents whether a doctor had ever told them they have a given condition, a reliable measure given the frequency with which older persons visit physicians. Activities of daily living (ADL), meanwhile, was assessed using a ten-item instrument adapted from the RAND 36-Item Short Form Health Survey (Ware and Sherbourne 1992). The items asked respondents whether they were limited in each of ten proffered domains a lot, a little, or not at all. The domains were: vigorous activity; moderate activity; lifting or carrying groceries; climbing several flights of stairs; climbing one flight of stairs; bending, kneeling, or stooping; walking more than a mile; walking several blocks; walking one block; and bathing or dressing yourself. From these items, a rescaled mean score of zero to one was assigned. This coding forces the range of the ADL scores to be the same as the illness categories. This allows for crude comparability among the health variables. In a supplementary model, self-rated health was used as an additional point of comparison. Respondents were asked, "In general, would you say your health is excellent, very good, good, fair, or poor." This variable serves as a useful composite of physical health problems that is suitable for a linear regression model. Versions of linear regression, including a model that that allows for the direct estimation of gene \times environment interactions, form the bulk of the analysis.

Methods

The analysis of twin pairs presents unique opportunities, but this study is not only interested in genes. I employ a two-part strategy. In the first part, I look at the determinants of health and well-being at the individual level using a sample of twins, but keeping the unit

of analysis the individual rather than the pair. The models adjust the standard errors for the nesting that occurs at the level of the family. In one model, the models also adjust for family fixed-effects, thereby controlling for everything twins within a pair have in common. This provides a very high degree of control. The models are either linear regression models or logit models, depending on the dependent variable, although because most of the models apply to depression, most of the models are linear.

The second part of the analysis uses the classic twin-design approach for estimating heritability, but retains the linear regression framework. Linear regression is familiar to virtually all sociologists, but can easily be extended to allow for the direct estimation of heritability and, more importantly, for the direct estimation of interactions between heritability and any factor included on the right-hand side as an independent variable. A secondary purpose of this article is to introduce medical sociologists to a research strategy for analyzing genetically informative data using the conventional tools of the discipline.

The model was initially developed by DeFries and Fulker (1985) and extended by Labuda, DeFries, and Fulker (1986). The model uses the twin pair, rather than the twin, as the unit of analysis. Each observation, thus, contains information on both proband and cotwin. The basic regression equation is as follows:

$$y = \beta_0 + \beta_1 P + \beta_2 R + \beta_3 E + \beta_4 PR + \beta_5 PE + \beta_6 RE + \beta_7 PRE + \varepsilon$$

Where y is the cotwin depression score, P the proband depression score, R the coefficient of relationship (i.e., .5 for DZ twins and 1 for MZ twins), and E the mean-centered education level of the cotwin. Specified in this fashion the coefficients directly represent all the quantities of interest: β_0 represents the intercept; β_1 represents the average environmentality, c^2 ; β_4 represents the average heritability, h^2 , equal to twice the difference between the MZ and DZ regression coefficients; β_5 represents the interaction between

education and c^2 and can be interpreted as the expected change in c^2 for a unit change in years of education; and β_6 represents the interaction between education and h^2 and can also be interpreted as the expected change in h^2 for a unit change in education (i.e., the gene \times environment interaction).

This method has much to recommend it. The key quantities, including average heritability, are represented as coefficients, whose significance can be evaluated in the conventional fashion of linear regression coefficients (i.e., whether the coefficient significantly different from zero). The gene \times environment interaction can also be interpreted in a direct fashion, showing percentage-point changes (after multiplying by 100) in average heritability for each additional year of schooling. In addition, the model allows for a vector of control variables, thereby improving the estimation of heritability and the interactions.

Results

Table 1 presents basic descriptive statistics for depression, averaged over the entire sample of twins. The table shows the mean for depression, the standard deviation, the median, and the kurtosis, which is used to describe the skew that is common to measures of depressive symptoms. These statistics are presented for the overall sample and for the three select education groups. This set of statistics conveys four things: first, the mean level of depression is quite low, .145, meaning the average number of symptoms is just over two (.145 \times 15), and the mode, found in 28% of the sample, is zero; second, depressive symptoms are skewed, meaning very few report a large number of symptoms; third, there is a negative relationship between education and depression; fourth, the skew of the distribution increases over additional levels of education. The well-educated are more assured of avoiding depression.

--Insert Table 1 and Table 2 About Here--

The remaining results are based on inferential models and proceed across four tables. Table 2 shows the relationship between education and depression based on a linear regression model. The first two models adjust the standard errors for clustering by family, while the third model adjusts for family fixed-effects, thereby holding constant everything twins have in common, including genes. This provides a very strenuous test of a causal effect, as it controls for a great many unobserved covariates, although it can be considered conservative in the sense that it relies on twin-pair differences, which can be small, especially in the presence of strong genetic influences. The table presents other specification tests. The first model specifies the relationship between education and depression using a linear years-of-schooling covariate, while the second specifies the relationship using three degree-based categories. Model BIC statistics are presented to assess the relative fit of these two specifications. The best fitting model is Model 1, with a simple linear term for years schooling, although regardless of the specification both models reach the same conclusion: education is significantly related to depression in later life. Some comparisons are useful for assessing magnitude. A year of additional education yields approximately the same change in depression as expected from a year of aging, albeit in different directions. Similarly, the relationship between marriage and happiness is quite strong. Using Model 1 as a baseline, the total difference between those married and those never married, divorced, or separated (.043 units) is equivalent to a little more than 8 years of schooling. Using Model 2 instead, the difference between a college graduate and high school dropout is very similar to the effect of marriage. Widowhood is positively associated with depression although the difference is not statistically significant, perhaps reflecting a mix of recent widowers and those whose spouses died years earlier. Model 3 includes family fixed-effects. The coefficient for education remain

significant and is reduced only a small amount relative to a model that does not adjust for the great many influences shared by twins (from -.005 to -.004). It may be true that the relationship between education and depression declines over the life course, but it nonetheless remains strong in later life.

--Insert Table 2 About Here--

Table 2 sets the baseline for the relationship between education and health, but Table 3 moves a step closer toward an explanatory model. Table 3 presents information necessary for evaluating the potential mediating effects of poor health. It presents five things: (i) the mean of the five health variables; (ii) the relationship between these variables and education, expressed as the education coefficient from a logit model (hypertension, heart attack, stroke, diabetes) or linear regression model (ADL) predicting the health variable; (iii) the relationship between the health variable and depression, expressed as the health variable coefficient from a linear model predicting depression; (iv) the percent of the education-depression relationship explained by the health variable, based on the reduction of the education coefficient between a model without and with the given health variable; and (v) the percent of the age-depression relationship explained by the health variable, based on the same.

--Insert Table 3 About Here--

The table reveals, first, that health problems are common in this age group. The most common disease is hypertension, found in 44% of respondents, but even the least common illness is found in nearly 10%. About 58% of respondents have either hypertension, a past heart attack or stroke, or diabetes (result not shown). The average ADL score is .24, from a range of zero to one. Only 11% of the sample reports none of the limitations included in the ADL battery (result also not shown). The next row presents the relationship between education and each of the health variables. Consistent with research showing a decline in the

relationship between social factors and health with age, the relationship between education and most of the health variables is small and, in two cases, statistically insignificant.

Education reduces the likelihood of hypertension and diabetes, although it is not significantly associated with a stroke or heart attack (perhaps, though, reflecting greater survival from these events). Exponentiating the logit coefficients reveals that each additional year of education reduces the odds of hypertension by about 2% and diabetes by about 4%. The strongest relationship is with the ADL score, where education strongly reduces the severity of these limitations. This relationship is the most significant of the set, at least based on the ratio of coefficient to standard error.

Nonetheless, all of the health variables are strongly related to depression. These coefficients are quite large. Comparing these coefficients with the married coefficient presented in Table 2, the models suggest that poor health is as or more damaging than being never married, divorced, or separated (recall the marriage coefficient was $-.043$). It is difficult to compare the four categorical, present/absent, illnesses with the continuous ADL score, although they do share the same range. Allowing for this incompatibility in measurement, the relationship between ADL and depression is still very large. Traversing the range of the ADL score results in an increase in depression that is at least six times larger than the difference between, for example, having a heart attack and not ($.289/.045$).

The importance of poor health is even more apparent in the next row, where I present the percent of the education-depression relationship that can be explained by each of the health variables. Overall the mediating effects of the four illnesses are quite weak, but the mediating effect of the ADL score is very large, whether with respect to education or even age. Activities of daily living explain about 72% of the relationship between education and depression and 81% of the increase in depression between ages 70 and 82. The nearest

competitor is stroke, which explains about 10% of the increase in depression over this age range, and diabetes, which explains about 5% of the education-depression relationship. In other words, the well-educated are able to avoid depression in later life not so much because they avoid poor health altogether as they prevent the health problems they develop from affecting their daily activities. The relationship between age and depression is also largely a function of the social consequences of illness.

--Insert Table 4 About Here--

Table 4 puts these results in a genetic context. Up until this point, the models have been largely insensitive to the relatedness of twins, apart from a standard-error correction and the use of family fixed-effects. Table 4 presents a basic heritability model (Model 1), as well as a gene \times environment model, exploring, in particular, the moderating effects of education (Model 2). Model 1 shows the strong heritability of depression in later life. The estimated average h^2 is .305 over the entire sample. Model 2, however, reveals a very strong gene \times education interaction. Because education is mean-centered, Model 2 shows approximately the same average heritability at the mean (zero) level of education ($h^2 = .308$), but, more importantly, also shows that for each additional year of education the heritability of depression decreases by .067 points. Multiplying by 100 allows for a simple percentage-point interpretation. Figure 1 presents predictions between the 10th and 90th percentile of education, as well as the estimated heritabilities from a version of Model 1 specified for the three degree-based subsamples. This allows for a test of the possibility that a linear term for education, while appropriate from the standpoint of model fit, misstates the magnitude of the gene \times environment interaction. The figure shows that regardless of how education is specified, the interaction is large, revealing a heritability of 50% or more for those with less than a high school degree, just under 50% for those with a high school degree or some

college, and virtually 0% for those with a four-year college degree. Education also increases the relevance of common environments, although the positive interaction coefficient is statistically indistinguishable from zero. Altogether the model overall suggests that depression is almost entirely a product of unique environment for those with a college degree.

--Insert Figure 1 About Here--

This genetic moderation by education is specific to depression. It does not reflect a more general process wherein the well-educated are able to avoid the deleterious effects of genes over all common illnesses of aging. Table 5 presents the same education \times gene interaction model, but for activities of daily living and self-rated health, used here as a convenient and linear composite of various physical illnesses. Recall that the ADL score explained most of the relationship between education and depression. It is plausible that education also reduces the influence of genes on ADLs and, therefore, that the gene \times environment interaction for depression actually pertains only to a specific mediating mechanism. Model 1 suggests, however, this is not the case. ADL scores show moderate heritability ($h^2 = .22$) and this heritability is not moderated by education. Education does not moderate the influence of genes on self-rated health either, although the influence of genes on self-rated health is considerably higher than on ADL scores ($h^2 = .41$). As a compensating gene \times environment interaction, then, the interaction appears to be specific to depression.

--Insert Table 5 About Here--

Discussion

Interpreting the effects of education on depression requires a simultaneous appreciation of several things. First, education is negatively related to later life depression.

Second, much of this association can be explained not by better health *per se*, but by lower levels of health-related impairment in activities of daily living, even though common vascular illnesses do increase depression regardless. Third, education reduces the heritability of depression, although this reduction is especially pronounced among those with a four-year college degree. Altogether these relationships suggest education works in a compensatory fashion, mitigating the influence of genes. It also points to the relevance of an especially enhanced environment rather than a particularly deleterious environment, as would be suggested by interactions that are pronounced on the other end of the educational spectrum (Shanahan and Hofer 2005). For this cohort of men, college education was made possible by the GI Bill. A college-degree would afford them a much more enriched environment over a life span than that available to those with less education, although there were also many opportunities for those with a high school degree. In this sense, advanced education can be seen as providing a markedly more positive environment and, thus, one capable of compensating for the otherwise large genetic risks for later life depression. Advanced education does not, however, seem able to reduce the genetic risks for other physical illnesses. The powerful genetic risks for poor physical health appear in both the “average” environment and the “enriched” environment. There is no gene \times environment interaction. It is useful, then, to think about later life depression as a particular phenotype that does not share some critical features with the genes for poor health, even though poor health and depression are related. There are several possible interpretations of these patterns.

For one, it is possible that education cannot forestall the risks of poor physical health altogether, but the well-educated might have other resources to promote positive psychological experiences even as health deteriorates. The literature on successful aging is helpful in this regard. One possibility is that the well-educated are able to blunt the effects of

poor health on their environment, if not always the onset of illness itself. As noted, education is strongly related to lower impairments in activities of daily living. Although education does not reduce the genetic risks for these impairments, it is notable that activities of daily living are largely a product of the environment for all education groups (the heritability is less than that found for depression). Supplementary models (not presented above) found no evidence for an interaction between education and each of the four illnesses in a model predicting ADL scores, although such an interaction was found when using self-rated health as an independent variable instead. In other words, the relationship between self-rated health and limitations in activities of daily living is weaker for the well-educated. In addition, the literature points to the offsetting effects of psychological resilience. It is possible that skills of this type are much more common among the well-educated. The literature on aging shows the value of some specific interventions against late life depression, including focused psychological interventions such as life review and training in problem solving (Fiske, Wetherell, and Gatz 2009). A particularly effective strategy is related to health-engagement control strategies, or the use of strategic behaviors for meliorating the stress sequela of illness (Wrosch et al. 2007). The well-educated may be in a better position to prevent depression using a comparable set of methods.

In interpreting a gene \times environment interaction it is appropriate to focus on both sides of the interaction. For those with *less* education, later life depression appears to be mostly a reflection of genes. There are several interpretations for this. For one, the less well-educated may be more subject to the natural increase in poor health with age, producing some symmetry between the genetic risks for poor health and those for depression. Another interpretation is related to the natural history of depression. It is possible that depression among the less well-educated represents the continuation of an earlier case rather than the

onset of a new one. Relative to those with late-onset depression, those with early-onset depression are more likely to have a family history of the disorder, potentially indicating a stronger genetic component (Heun et al. 2001). If this is the case, the differences in heritability of depression between levels of education could reflect different underlying entities rather than fundamentally different processes. It is notable, however, that more than half of all cases of later life depression represent first onset cases (Fiske, Wetherell, and Gatz 2009), so the typical case of depression in later life is likely to be the kind that can be interpreted in reference to contemporaneous conditions.

Although this study focuses on education and depression, it draws attention to other determinants. In particular, it confirms the central importance of impairments in activities of daily living. Cardiovascular disease and diabetes are also related to depression, as expected, but activities of daily living has among the strongest effects, both in terms of its direct relationship with depression and its mediating effects in the education-depression relationship. Remarkably, it also explains most of the increase in depression by age, at least over this age range. In assorted ways, then, this study points to the importance of environmental influences. The relevance of the environment may be more indirect and interactive than the constellation of physical and cognitive impairments recent research has focused on, but this does not make it any less important.

Limitations and Caveats

It is important to recognize the particularities of the NAS-NRC registry and the assumptions of this analysis. Although the registry collected data over multiple waves, this study uses cross-sectional data. Genes and environment interact in dynamic ways over the life course, but this study was only able to infer processes at one point in time given that depression was only observed once. The influence of education likely reflects the

accumulation of many resources over the life course, rather than anything it might provide at any one time. In the same vein, the design does not reveal what it is about education matters. The study demonstrates the centrality of education in conditioning the heritability of depression, but it does not isolate what it is about education that does so. The influence of education on life chances is pervasive, so the set of potential explanations is large. On the flip side, it is also unclear what specific genes are implicated in the interaction, although the results make clear the gene \times environment interaction does not apply to all genes related to health.

Of course, the current study is also limited to men of a very specific cohort who served in the armed forces during the greatest conflict of their time. It is unclear whether the patterns observed here also apply to women or to other racial/ethnic groups. It is also unclear whether the gene \times environment interactions found here are equally strong among other cohorts or at points earlier in the life course. It is possible the influence of education over genes is only apparent later in life when the cumulative benefits of education have been realized. It is also possible the interactions are most pronounced when the average variation in environments between education groups is particularly large. Over time the average environment for the entire population may be moving closer to the sort of environment found only among the college educated among this particular cohort. Despite the difficulty of balancing such considerations, understanding gene \times environment interactions requires as much appreciation of history as the life course.

It is also worth emphasizing that heritability is fundamentally a population-level estimate. It refers to the proportion of variance in a population for a given phenotype that can be explained by genetic variation within that population. Gene \times environment interactions, meanwhile, imply individual-level processes. There may be some overlap

between individual-level and population-level processes, but the interactions documented here properly refer only to the latter, that is, the amount of variation in depression that can be explained by genes for specific educational groups. Molecular investigations applied to individuals may not yield the same findings, but the results point to the value of pursuing such studies.

Conclusion

Avoiding depression is an important element of successful aging. Research on the topic has grown enormously over the years, and there has been increasing recognition that successful aging may be at least partly genetic (Depp, Vahia, and Jeste 2010; Vaillant and Mukamel 2001). The present study suggests that depression is indeed strongly heritable, but also that it might not be heritable under the right environmental conditions. Although it is popular to regard mild depression as a natural feature of aging, or to see negative genetic influences later in life as the price we pay for good health earlier in life, the present study indicates the biology of aging is not enough to supersede the influence of an enhanced environment.

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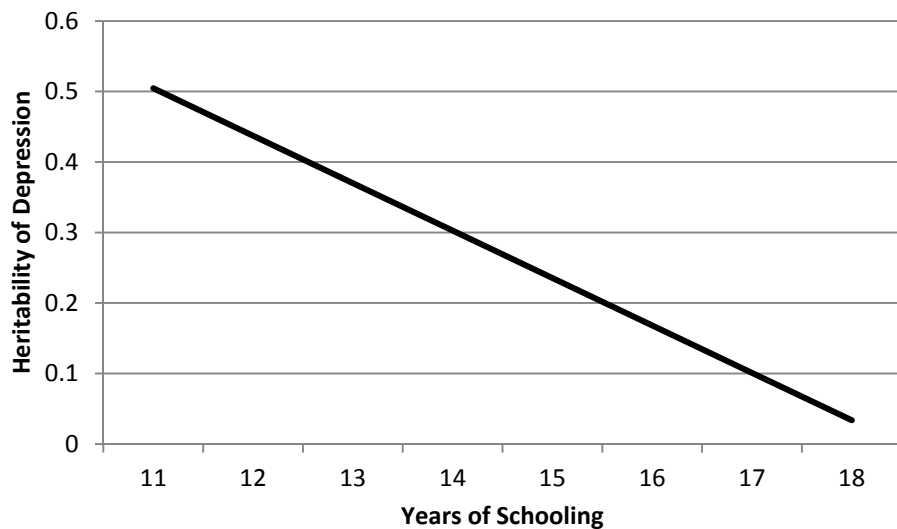
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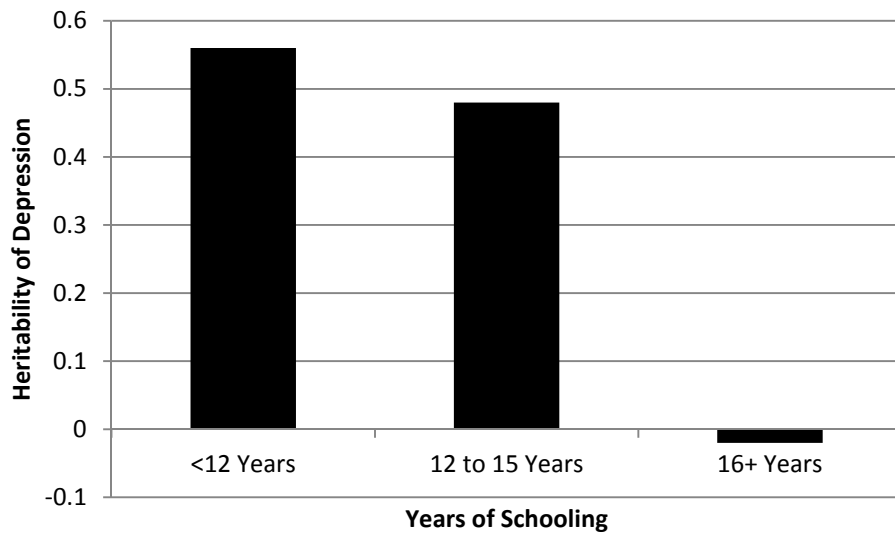
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Figure 1. Gene \times Education Interaction Predicting Depression (NAS-NRC Twin Registry of World War II Veterans)

Panel A.



Panel B.



Note: Estimates based on models presented in Table 4.

Table 1. Summary Statistics for Depression (NAS-NRC Twin Registry of World War II Veterans (N = 3,710))

	Mean (Range 0-1)	Standard Deviation	Median	Kurtosis
Overall	.145	.162	.077	7.498
Years of Education < 11	.180	.173	.133	5.711
Years of Education 12 to 16	.151	.166	.133	7.281
Years of Education 16+	.125	.148	.067	8.960

Table 2. Regression Models Predicting Depression (NAS-NRC Twin Registry of World War II Veterans)

	Model 1	Model 2	Model 3
Education (Years of Schooling)	-.005*** (.001)		-.004* (.002)
Schooling 12 to 15 Years		-.027** (.009)	
Schooling 16+ Years		-.050*** (.009)	
Age	.004*** (.001)	.004*** (.001)	
Married	-.043*** (.011)	-.044*** (.011)	-.037** (.013)
Widowed	.004 (.015)	.003 (.015)	-.005 (.017)
Constant	-.145	-.118	.176***
BIC	-3049	-3039	
Twins	3710	3710	3710
Twin Pairs	1855	1855	1855
Family Fixed Effects	No	No	Yes

* $p < .05$; ** $p < .01$; *** $p < .001$ (standard errors in parentheses)

Note: Models 1 and 2 adjust the standard errors for family clustering.

Table 3. Summary Statistics and Relationships between Education and Health Variables (NAS-NRC Twin Registry of World War II Veterans)

	<i>Health Variable</i>				
	Hypertension	Heart Attack	Stroke	Diabetes	ADL
Mean of Health Variable	.44	.16	.09	.14	.24
Relationship with Education (education coefficient from regression model predicting health outcome)	-.023* (.012)	-.027 (.015)	-.011 (.018)	-.041* (.016)	-.014*** (.001)
Relationship with Depression (health variable coefficient from regression model predicting depression)	.029*** (.005)	.045*** (.008)	.070*** (.012)	.051*** (.009)	.289*** (.014)
Percent of Education-Depression Relationship Explained by Health Variable	3%	3%	1%	5%	72%
Percent of Age-Depression Relationship Explained by Health Variable	1%	4%	10%	1%	81%
Twins	3710	3710	3710	3710	3710
Twin Pairs	1855	1855	1855	1855	1855

* $p < .05$; ** $p < .01$; *** $p < .001$ (standard errors in parentheses)

Note: Categorical outcomes modeled using logit regression. Depression modeled using linear regression.

Table 4. Gene \times Environment Linear Regression Model Predicting Depression (NAS-NRC Twin Registry of World War II Veterans)

<i>Covariate</i>	<i>Interpretation</i>	Model 1	Model 2
Proband Depression	Average c^2	-.060 (.073)	-.062 (.073)
Coefficient of Relationship		-.096*** (.020)	-.098*** (.020)
Education		-.005*** (.001)	-.013* (.005)
Proband Depression \times Coefficient of Relationship	Average h^2	.305*** (.092)	.308*** (.092)
Proband Depression \times Education	Education $\times c^2$.037 (.023)
Coefficient of Relationship \times Education			.014* (.006)
Proband Depression \times Coefficient of Relationship \times Education	Education $\times h^2$		-.067* (.029)
Constant		-.004	-.009
Twin pairs		1855	1855

* $p < .05$; ** $p < .01$; *** $p < .001$ (standard errors in parentheses)

Note: All models include controls for age and marital status.

Table 5. Gene \times Environment Linear Regression Model Predicting ADL and Self-Rated Health (NAS-NRC Twin Registry of World War II Veterans)

<i>Covariate</i>	<i>Interpretation</i>	Model 1 ADL	Model 2 Self-Rated Health
Proband Dependent Variable	Average c^2	.024 (.071)	-.104 (.073)
Coefficient of Relationship		-.098** (.031)	-1.341*** (.330)
Education		-.001 (.008)	.144 (.080)
Proband Dependent Variable \times Coefficient of Relationship	Average h^2	.223* (.090)	.406*** (.092)
Proband Dependent Variable \times Education	Education $\times c^2$	-.032 (.024)	-.026 (.022)
Coefficient of Relationship \times Education		-.009 (.010)	-.103 (.102)
Proband Dependent Variable \times Coefficient of Relationship \times Education	Education $\times h^2$.023 (.030)	.030 (.028)
Constant		.272***	3.773***
Twin pairs		1855	1855

* $p < .05$; ** $p < .01$; *** $p < .001$ (standard errors in parentheses)

Note: All models include controls for age and marital status.

Appendix A: Geriatric Depression Scale (GDS-15)

All response categories yes or no

1. Are you basically satisfied with your life?
2. Have you dropped many of your activities or interests?
3. Do you feel that your life is empty?
4. Do you often get bored?
5. Are you in good spirits most of the time?
6. Are you afraid something bad is going to happen to you?
7. Do you feel happy most of the time?
8. Do you often feel helpless?
9. Do you prefer to stay at home rather than going out and doing new things?
10. Do you feel you have more problems with memory than most?
11. Do you think it is wonderful to be alive?
12. Do you feel pretty worthless the way you are now?
13. Do you feel full of energy?
14. Do you feel that your situation is hopeless?
15. Do you think that most people are better off than you are?