C.A. Rietveld, D. Cesarini, D.J. Benjamin, P.D. Koellinger, J-E De Neve, H. Tiemeier, M. Johannesson, P.K.E. Magnusson, N.L. Pedersen, R.F. Krueger, M. Bartels

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Molecular Genetics and Subjective Well-Being

Cornelius A. Rietveld[a], David Cesarini[b,c], Daniel J. Benjamin[d], Philipp D. Koellinger[a], Jan-Emmanuel De Neve[e,f], Henning Tiemeier[g], Magnus Johannesson[h], Patrik K.E. Magnusson[i], Nancy L. Pedersen[i], Robert F. Krueger[j,1], Meike Bartels[k,l,1]*

[a] *Department of Applied Economics, Erasmus School of Economics, Erasmus University Rotterdam.*

[b] *Center for Experimental Social Science and Department of Economics, New York University.*

[c] *IFN-Research Institute for Industrial Economics, Stockholm.*

[d] *Department of Economics, Cornell University.*

[e] *School of Public Policy, University College London.*

[f] *Centre for Economic Performance, London School of Economics and Political Science.*

[g] *Department of Epidemiology & Biostatistics, Erasmus Medical Center.*

[h] *Department of Economics, Stockholm School of Economics.*

[i] *Department of Medical Epidemiology and Biostatistics, Karolinska Institutet.*

[j] *Department of Psychology, University of Minnesota.*

[k] *Department of Biological Psychology, VU University Amsterdam.*

[l] *EMGO+ Institute for Health and Care Research, VU University Medical Center, Amsterdam*

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*To whom correspondence should be addressed: Meike Bartels, Department of Biological Psychology, VU University, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands. E-mail: m.bartels@vu.nl

[1] *These authors contributed equally to this work.*

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.

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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 (1-2). SWB is conceptualized to include a continuous spectrum of positive feelings and subjective life assessments (3-5). 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 (6-7). 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 (8). Most of the literature examines social, economic, and psychological influences on SWB (4, 9), 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 (10-17). 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 (18).

So far, however, the few attempts to find genetic polymorphisms associated with SWB have been unsuccessful (see (19) for the earliest effort we know of). One study reported an association (20), but follow-up work on an augmented sample from the same data did not replicate the finding (21). 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 (22-23).

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 (21), which complements what can be learned from twin and family studies (22-24). 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 (25-26), 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 (27); for a critical perspective, see 28). 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 (29) 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 30). 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 (14,16).

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 (31-32) called **G**enomic-**R**elatedness-Matrix **Re**stricted **M**aximum **L**ikelihood, or GREML. We apply GREML to SWB, pooling data from two large datasets, TwinGene (TG; the genotyped subsample of the Swedish Twin Registry (33)) and the Rotterdam Study (34), 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 (31), intelligence (35-36), personality traits (37), several common diseases (38), schizophrenia (39), economic and political preferences (22), as well as smoking, glucose levels, and depression (40). 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; see Materials and Methods). 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 (41), 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 (42)). This assumption might be violated if the sample includes members of a common 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 (43), 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 (32) that we use for the GREML analysis cannot presently handle multinomial variables, we converted the responses to binary variables (for details, see Materials and Methods).

Results

Table 1 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). Figure 1 shows the estimates and standard errors for the pooled

sample. These estimates 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.

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 1.

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 (that 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.

In the Supporting Information, we report results of additional analyses that examine how sensitive our baseline results are to the choice of relatedness thresholds and to whether relatedness is estimated only using SNPs available on both platforms (see Table S3 in the SI). Reassuringly, these estimates are very close to those in our preferred specification. We also attempted to compare the GREML estimates to conventional twin-based estimates, when both are derived from the Swedish twin sample. The twin estimates, shown in table S4, are in the same range as the GREML estimates, but unfortunately we cannot draw strong conclusions because the twin estimates are very imprecise.

Discussion

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 (16)). 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 (29). Twin-based analyses tend to produce heritability estimates for personality around 30-50% (44-45), but a recent study finds evidence that a substantial share of the heritability of Neuroticism, Openness, and Agreeableness is due to non-additive factors (46). 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 (37), respectively, and another reports estimates in the range 4-10% for traits assessed by the Cloninger personality inventory (47).

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 (48). 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 (49).

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 (50) and 80-90% for height (51). 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 (52) and 60% for height (53). By comparison, the one published GREML estimate for height is 45% (31), and GREML estimates for cognitive ability have also been around 45% (35-36). 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 (54)). 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* (8) 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 (42) 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 (11) 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 (55) 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 (54) 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.

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; see (33)). A subsample of SALT was recently genotyped using the Illumina HumanOmniExpress BeadChip technology as part of the TwinGene project (22). 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 (see (34)). ~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.

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

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to one half, thereby maximizing the variance and hence statistical power. The distributions of SWB measures before they were binarized are given in Table S1.

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 S2 in the SI Appendix 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.

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Figure Legends

This figure shows the GREML estimates, and their 95% confidence intervals, for *Happy*, *Enjoy*, and *Combined*. The sample pools the three Rotterdam cohorts (RS) and the Swedish Twin Registry TwinGene sample (TG).