Heritability of health and aging limitations on personally desired activities

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Abstract

The aim of this study is to estimate heritability of incident limitations on personally desired activities within the eighth decade of life. We measured self-rated ability to perform ten personally desired activities in 1606 male veteran twin pairs at baseline and four years later. At follow-up, 33% of the cohort reported more limitations in desired activities. Among twins who completed both assessments, there were no statistically significant differences in incidence rates of limitations as a function of zygosity. Sensitivity tests showed the same for change scores; and that, if cognitive impairment or death are deemed to belong among limitations of desired activities, zygosity contributed 10% to new limitations at follow-up. Maintaining personally desired activities over four years in the eighth decade is not subject to substantial genetic influence. However, if death and cognitive impairment are added to incident limitations, then genetics plays a modest role. In all cases, unique environment is the predominant influence.

Introduction

With increasing longevity and the aging of the baby boomer cohort, the oldest age groups (over 85) are projected to increase considerably by 2030, raising concerns about the level of their dependency, health service needs, and quality of life.[1] It is therefore of considerable interest to examine the course and determinants of components of quality of life in the period after age 70 that is the gateway to very old age. Being able to choose to engage in one's desired activities is integral to several definitions of quality of life, for example, successful aging and active life expectancy.[2,3] The ability of aging adults to maintain personally desired activities is influenced to an uncertain extent by genetics: at issue is what room the genetic influence leaves for preventive intervention and life style to maintain desired activities.

There are well-tested methods for detecting and estimating the strength of the heritability impact on aging, including searching for accumulation of candidate genes or familial patterns in long-lived groups, and comparing similarities or dissimilarities in identical and fraternal twins. Moreover, search strategies have become increasingly sophisticated, for example Genome-Wide surveying, such as Association Studies (GWAS) and complex trait analysis (GCTA).[4] Nevertheless, an emphasis on the heritability of aging *changes* (*i.e.*, incidence of new declines) in functioning is not addressed by prevalence estimates at points in time; incident changes are needed.

An attenuation of genetic influence in late life is to be expected according to theory proposed by Kirkwood and Austad amongst others.[5,6] Consistent with that prediction, McArdle and Plassman found in the Duke Twins Study of Memory in Aging that genetic influence on changes in memory was evident with multiple assessments over 12 years after 70 years of age,[7] but not beyond the midpoint of the eighth decade. McGue and Christensen (2002)[8] had similarly concluded in the Longitudinal Study of Aging Danish Twins (nearly 1000 twin pairs) that cognitive abilities in those 70 years and older showed generally high heritability, but cognitive change did not. Christensen *et al.*[9] reported that functional abilities as well showed generally high heritability, but that change in functional ability over time among the Danish Twins was not highly heritable. Shih-Fan Lin *et al.*[10] conducted trend analyses on data from the National Health Interview Survey from 1982-2009, and pointed to a surprising increase in disability of recent cohorts 70 years and older; they call for further study of this trend. There is as yet no replication of the heritability findings on functional abilities.

Materials and Methods

Sample

Participants were members of the Duke Twins Study of Memory in Aging based on the NAS-NRC Twin Registry of WWII Veterans under the National Academy of Sciences-National Research Council.[11] This Registry comprised 15,924 male twin pairs who had each served in the armed forces. Zygosity was determined from profiles drawing upon military records of physical characteristics, fingerprints, blood groups, and questionnaires about childhood similarities. In a subset of twin pairs, zygosity was estimated by cross-validation between profiles and gene typing to be 95% correct.[12]

Beginning in 1990, there were four waves of data collection approximately at three to four year intervals.[13] The third wave (W3) of the telephone survey of surviving and consenting twin pairs was carried out from 1996 to 1998, at ages 70 to 80 years (average 73.32 for monozygotic, standard error 0.06; 73.41 for dizygotic, standard error 0.06); and the fourth wave (W4) interviews were four years later. The telephone interview included a measure of cognitive status and a scale of Health Limitations of Personally Desired Activities (HLA) targeting eight explicitly desired activities,[14-17] and two items on limits on walking and on expressed need for assistance. All of the HLA items, except walking and need for regular assistance, were asked *Does your health stop you from doing* (*activity*) *as much as you would like?* For regular assistance: *Do you need anyone to regularly assist you in looking after yourself?* For walking: *How many city blocks, or the equivalent, can you walk without a rest?* All items were affirmative-negative

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Contributions: BJG designed the sub-study on changes in personally desired activities; BLP directed the host study that collected data on cognitive and functional changes in veteran twins; WP conducted the analyses on the effects of attrition; BS and JJMA analyzed transitions in personally desired activities.

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dichotomies, except number of blocks, which was dichotomized as <10 or 10+ for analyses. The telephone interview was completed by the participants or by a proxy informant if the participant could not complete it.

Statistical analyses

The analysis is designed to estimate the extent to which deterioration of HLA function, measured as changes from W3 to W4 resulting in new (main analysis) or increased (sensitivity analysis) health imposed limitations of desired activities, is influenced by genetics, shared environment, and non-shared environment factors. The HLA multi-item index is a sum of the number of desired activities limited by health, with each of the activities rating 0 or 1. All models were run in Mplus or M,[18,19] included baseline age as a covariate, with a longitudinal-biometric latent curve model for detection of effects on incidence and with use of an orthogonal decomposition of variance components for levels and slopes: these models employ simultaneous estimation of standard biometric parameters for twin models.[20-23] The models provide flexibility with regards to the outcome measures, in terms of whether they are measured in continuous or discrete categories. Prior to the main analyses, we conducted confirmatory factor analyses on the HLA items for one twin at W3 to see whether they could be constructed as a simple composite or whether some items were more influential than others. The results showed that the model constrained factor loadings of each of the items to 1, thereby indicating that a simple composite would fit the data well ($\chi^2(27)=54.53$, P<0.001, CFI=0.992) and did not provide a worse fit to the data when the factor loads were allowed to be freely estimated ($\chi^2(27)=53.09$, P<0.001, CFI=0.990).

Results

Sample attrition

The parent sample for the present analysis of changes in HLA consists of 2722 twin pairs (5444 individuals) who had responded to W3 interviews.[24] Of those, a total of 3807 individuals also responded at W4: The average time between W3 and W4 for these individuals was 4.49 years. This group was made up of 595 twin singletons and 3212 partners (1606 complete twin pairs). The response rate for twins whether paired or not is 70% (3807/5444), while the paired response rate is 59% (1606/2722). The twins who had died or become cognitively impaired were a substantial part of the sample attrition as there were 1003 deaths of twin individuals, as well as 95 twin individuals who were cognitively impaired at the follow-up assessment (total of 1098 twin individuals).

Incident limitations

Incidence represents the number of persons who did not report any limitations initially (at W3) but did report a *new* limitation at the second measurement point (at W4), while concordance represents the proportion of cases where both or neither of the twins reported a new limitation. The sample sizes (Table 1) for the incidence approach ranged from 1518 to 1602 (median: 1592) for all health limitation items except for the walking blocks item, which was 1178. Table 1 also displays prevalence, incidence and proband-wise concordance rates by zygosity, and Table 2 shows variance component estimates (in %) for liability for a given HLA item. There was considerable variability between items in the incidence of new limitations, with over 40% of persons reporting a new limitation in terms of their ability to walk more than 10 blocks (a sensitive or early indicator of health limitation), but less than 10 percent of persons reporting new limitations for getting about, light chores, traveling, or social activities (later or more advanced health limitations).

Table 2 presents the results of the twin pair analyses and provides estimates of the contributions of additive genetics, common environment, and unique environment for each of the activities at baseline (W3 prevalence), follow-up (W4 prevalence), and the incidence of a new limitation (difference). As noted in the table, several of the estimates were fixed at zero. This was due to the models not arriving at a final solution when these parameters were unconstrained on account of the variance estimates being too small to estimate, which is indicative of zygosity having little impact on incidence rates. In these instances, we applied the recommended correction of fixing (or constraining) those parameters at zero before rerunning the model and estimating the remaining parameters. Statistical fit indices were compared across the constrained and unconstrained models and no significant loss in model fit was observed. No statistically significant differences were present for incidence rates of new impairments as a function of zygosity.

Sensitivity analyses

Estimating the comparability with the prior study

In order to confirm that the analysis of incidence was comparable in sensitivity to methods used in our previous study of prevalence, we determined that additive genetics was statistically significant for prevalence of several of the items at both time points including leisure activities at W4, heavy chores at W3 and W4, holding a job at W3, getting about at W4, travel at W4, and social activities at W4 (Table 2). The amount of variance in prevalence rates accounted for ranged between 15% and 27%, comparable to our previous findings at W3.[24]

Estimating the degree of possible confounding due to attrition

In order to examine possible confounds introduced by non-responders, we carried out an additional analysis on the W3-W4 transition cohort. To account for missing data on some items, we converted partial sum scores proportionately to full scores when there were 6 or more reported HLA items. For those twins whose W4 HLA scores were missing because of death or cognitive impairment, we assigned a transition score of *worse* (*i.e.*, we equated the outcomes of death or cognitive impairment with maximal limitation of personally desired activities, following the convention reviewed by Brazier, 2005). Imputing a transition score of *worse* for these 1098 twin individuals resulted in an additional 411 twin pairs both of whom now had non-missing transition scores. With respect to twin pairs, this imputation process increased the twin pair response rate substantially (from 59%, 1606/2722, to 74%, 2017/2722 twin pairs). Subjects who refused to participate (n=539) were not included in our analyses. The estimation of genetic and environmental effects on W3-W4 changes without imputation of worse transition scores for the dead or cognitively impaired, gave essentially the same result as our primary analysis: neither additive genetics nor common environment have an appreciable effect on HLA items. With the imputation of *worse* transition scores for those dead or cognitively impaired, modest additive genetic and common environment effects were detected. The co-twin variance explained before replacement of missing subjects is here given first, followed by the result (in parenthesis) after replacement: A) additive genetics 4% (10%), C) common environment <1% (23%), and E) unique environment 96% (67%).

Accounting for subjects who were not free of restricted function at baseline

A change score (W4 minus W3) was computed for the 1606 twins (3212 individuals) who were alive and fully assessed, and neither of the twins in a pair was cognitively impaired at W3. At the follow-up point one third (33%) of the cohort had more limitation of activity, 20% had less limitation, and another 41% showed no change. Most of the changes were relatively small: 15% one point worse (higher score) and 18% more than one point worse; 12% one point lower (better) and 8% more than one point better. The odds ratio for increase of limitations for MZ=1.19 and for DZ=1.05, suggested that genes did not influence rates of change.

Discussion

In the current study, we examined the contribution of genetic and environmental influences on the development of new limitations in personally desired activities, for a sample of older veteran twins who were measured across a four-year follow-up period of their eighth decade. The results indicated that the development of limitations (incident or worse limitations) was largely related to unique environmental characteristics, and that common environment and additive genetics contributed little. This pattern was true for transitions across the range of initial (W3) and outcome (W4) scores, and also where both twins in a pair scored zero at W3 and one or the both scored either zero (no change) or 1+ at W4 (new or incident cases). Even though these decline projections may be understated by up to 20% because of reversals that may occur after the W4 assessments, nevertheless, the low heritability of longer-term decline in activity limitations is strongly suggested by the equivalence of MZ and DZ concordance rates for incidence changes between W3 and W4. Moreover, as the participants continue to age, we would anticipate that improvements in functional status become less common.[25]

There is considerable individual variability in the measurement of health limitations, requiring a strong signal for detection over this *noise*. A four year decline signal will not be as strong as an eight year decline signal, but the alternative of relying on projections of measurements at further points in time entails greater attrition of the cohort through deaths and other causes, and thus added uncertainty in projections. When attrition was reduced by assigning a *worse* limitations score to death or cognitive impairment, then a modest but significant impact of added genetics and shared environment emerged for a composite score of HLA items. This could have resulted from the increased size of the reconstituted sample, or from the proxy score assigned to death or cognitive impairment. Several twin studies have noted significant heritability for life expectancy,[26] with genes accounting for about a quarter of variance in length of life. [27]

In the current study, we were limited to two assessments across a four-year follow-up peri-

Table 1. Prevalence and incidence rates and Proband-Wise concordance rates by zygosity.

Items/time points*	MZ rates	MZ concordance	DZ rates	DZ concordance
Leisure activities (n)				
W3 prevalence (1600)	0.35	0.11	0.42	0.12
W4 prevalence (1598)	0.34	0.12	0.40	0.12
New limitation (1592)	0.21	0.06	0.25	0.08
Light chores				
W3 prevalence (1604)	0.08	0.01	0.10	0.03
W4 prevalence (1590)	0.11	0.06	0.11	0.02
New limitation (1588)	0.05	0.00	0.07	0.04
Heavy chores				
W3 prevalence (1598)	0.34	0.14	0.39	0.11
W4 prevalence (1587)	0.37	0.13	0.39	0.12
New limitation (1579)	0.20	0.07	0.22	0.05
Holding a job				
W3 prevalence (1570)	0.20	0.10	0.22	0.11
W4 prevalence (1551)	0.46	0.16	0.54	0.14
New limitation (1518)	0.09	0.04	0.08	0.00
Getting about				
W3 prevalence (1604)	0.10	0.04	0.12	0.02
W4 prevalence (1601)	0.19	0.10	0.24	0.06
New limitation (1599)	0.05	0.04	0.07	0.02
Heavy packages				
W3 prevalence (1596)	0.34	0.14	0.39	0.11
W4 prevalence (1579)	0.37	0.13	0.39	0.12
New limitation (1569)	0.20	0.07	0.22	0.05
Travel				
W3 prevalence (1604)	0.06	0.02	0.08	0.02
W4 prevalence (1601)	0.14	0.09	0.21	0.05
New limitation (1599)	0.03	0.03	0.05	0.00
Social activities				
W3 prevalence (1603)	0.04	0.03	0.07	0.04
W4 prevalence (1598)	0.09	0.07	0.10	0.03
New limitation (1595)	0.03	0.00	0.04	0.03
Cannot walk 10 blocks				
W3 prevalence (1525)	0.45	0.61	0.45	0.54
W4 prevalence (1228)	0.32	0.26	0.34	0.23
New limitation (1178)	0.42	0.27	0.42	0.22
Needs regular assistance				
W3 prevalence (1604)	0.02	0.00	0.01	0.00
W4 prevalence (1604)	0.08	0.03	0.07	0.04
New limitation (1602)	0.01	0.00	0.01	0.00

*Time 1=W3 and Time 2=W4. Sample sizes varied across the activities due to items that participants did not answer or respond *don't know*. The sample size for C*annot walk 10 blocks* is less than the other activities because there was a higher frequency of *don't know* responses for this item.

od. It seems that incidence declines in genetically influenced function and cognition may occur very slowly during the period of advanced aging, with a more detectable cumulative residue evident in prevalence.

Limitations

The sample is of male veterans, so the findings may not apply to females. Furthermore, selection of a sample based on military service can be viewed as a further bias, though it does clarify the interpretation of the findings: functional impairments in young adulthood resulting from birth injury, early expression of genetic abnormalities, and serious consequences of childhood or adolescent accidents or illnesses, are likely to have been excluded from this study by military selection standards.

Since genetic analyses require twin paired data to estimate correlations, and because response rates will inevitably be lower for pairs than for single twins, we assigned a proxy score for purposes of a sensitivity analysis, as described earlier: this raised the response rate to 74% and produced a modified result that is informative but complicated by the assignment of a score of *worse limitations of desired activities* as a proxy for death and cognitive impairment. A decline in health limitation scores from W3 to W4 does not firmly predict the further course of limitations: 20% of the scores at W3 were followed with improvement by W4, in line with several national longitudinal studies reporting that the declines of aging follow a steady course when aggregated and measured over long intervals, but are complicated by recovery and relapse when charted more frequently.[28]

The variation in rates of new limitations across the follow-up period is not unexpected since some of HLA activities are less demanding and more readily preserved. For example, leisure activities, carrying heavy packages, and walking 10 or more blocks are more difficult to maintain; at least 20% of these activities became more limited over time, whereas for other outcomes (*e.g.*, travel) less than 10% of individuals reported a change in status. These differences in the rates of incident impairments reduced the incidence rates of certain activities and therefore may have minimized the potential for genetic influences on outcomes.

These findings show that a male who is on

Table 2. Variance component estimates (%) for liability for a given function: additive genetics, common environment, and unique environment variance components.

Outcome/time points	Additive genetics	Common environment	Unique environment
Leisure activities (n)			
W3 prevalence	0.06 (-0.27-0.40)	0.06 (-0.20-0.33)	0.88 (0.76-0.99)
W4 prevalence	0.16 (0.06-0.27)	0[a]	0.84 (0.73-0.94)
Difference	0[a]	0.08 (-0.03-0.19)	0.92 (0.82-1.03)
Light chores			
W3 prevalence	**	**	**
W4 prevalence	0.17 (-0.02-0.35)	0[a]	0.84 (0.65-1.02)
Difference	0[a]	0.13 (-0.04-0.29)	0.87 (0.71-1.04)
Heavy chores			
W3 prevalence	0.24 (0.14-0.34)	0[a]	0.76 (0.66-0.86)
W4 prevalence	0.16 (0.06-0.26)	0[a]	0.84 (0.74-0.94)
Difference	0.08 (-0.06-0.22)	0[a]	0.92 (0.78-1.06)
Holding a job			
W3 prevalence	0[a]	0.28 (0.18-0.39)	0.72 (0.62-0.82)
W4 prevalence	0.15 (0.06-0.25)	0[a]	0.85 (0.75-0.94)
Difference	0.09 (-0.13-0.32)	0[a]	0.91 (0.68-1.13)
Getting about			
W3 prevalence	0.05 (-0.17-0.26)	0[a]	0.96 (0.75-1.17)
W4 prevalence	0.23 (0.10-0.36)	0[a]	0.77 (0.64-0.90)
Difference	0.22 (-0.03-0.48)	0[a]	0.78 (0.52-1.03)
Heavy packages			
W3 prevalence	0.16 (-0.15-0.47)	0.06 (-0.19-0.32)	0.78 (0.68-0.88)
W4 prevalence	0.19 (-0.09-0.48)	0.01 (-0.22-0.24)	0.79 (0.69-0.89)
Difference	0[a]	0.07 (-0.05-0.20)	0.93 (0.80-1.05)
Travel			
W3 prevalence	0.03 (-0.27-0.33)	0[a]	0.97 (0.67-1.27)
W4 prevalence	0.21 (0.06-0.36)	0[a]	0.79 (0.64-0.94)
Difference	0.21 (-0.59-1.00)	0.06 (-0.40-0.53)	0.73 (0.36-1.10)
Social activities			
W3 prevalence	0.02 (-0.92-0.96)	0.18 (-0.51-0.87)	0.79 (0.43-1.17)
W4 prevalence	0.27 (0.09-0.45)	0[a]	0.73 (0.55-0.91)
Difference	0.25 (-0.54-1.04)	0.08 (-0.69-0.85)	0.67 (0.57-0.77)
Cannot walk 10 blocks			
W3 prevalence	0.03 (-0.24- .29)	0.13 (-0.09-0.34)	0.85 (0.76-0.93)
W4 prevalence	0.15 (-0.19-0.48)	0.08 (-0.19-0.36)	0.77 (0.66-0.88)
Difference	0.06 (-0.04-0.16)	0[a]	0.94 (0.84-1.04)
Needs regular assistance			
W3 prevalence	0[a]	0.51 (0.45-0.57)	0.49 (0.43-0.55)
W4 prevalence	0[a]	0.13 (-0.06-0.31)	0.87 (0.69-1.06)
Difference	0[a]	0.18 (-0.01-0.37)	0.82 (0.64-1.00)

[a]Estimate fixed to zero. **All variance in unique environment when additive genetics and common environment fixed to 0: model cannot be estimated.

the brink of *old age*, but not currently limited in desired activities by health or age, is not at genetic risk for increasing restriction of desired activities with further aging. However, if death or cognitive impairment supervenes, and if the latter two outcomes are interpreted as being the equivalent of restriction of desired activities, then genetics will likely play a somewhat larger role. In both scenarios, the person's scope of desirable activity will be determined in large part by their unique environment, including life style patterns such as exercise, smoking, nutrition, and social and intellectual activity, as well as good public and personal health care.

These understandings are important in pointing to the scope for preventive and interventional health and social services to maintain quality of life in older ages, as well as motivating aging persons to take a proactive role in maintaining their capacity to choose desired activities, a crucial element in preserving quality of life in the extended life span that rising generations are enjoying.

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