A Twin Study of the Genetic Contribution to Age-Related Functional Impairment

Barry J. Gurland,1 William F. Page,2 and Brenda L. Plassman3

1Columbia University Stroud Center for Study of Quality of Life, New York.
2Institute of Medicine, Washington, District of Columbia.
3Department of Psychiatry, Duke University Medical Center, Durham, North Carolina.

Background. A key element in the quality of later life is the prevalence of age-related functional impairments. The objective of this study was to quantify the genetic and environmental influences on age-related functional impairment in a population of white male twin elders who were fit in young adulthood when entering military service. The extent of genetic influence on functioning in later life affects the role of public health, personal initiative, and service interventions.

Methods. Indicators of functional impairment were determined by telephone survey and by twin pair responses to 10 indicators of basic, instrumental, and social activities, and mobility. Responses were analyzed using structural equation modeling. Prevalence and concordances were determined by zygosity status. Covariance was partitioned between twins in a pair into components attributable to additive genetics, common environment, and unique environment.

Results. Data from 2721 twin pairs (1384 monozygotic and 1337 dizygotic) were analyzed for the 10 dichotomous indicators of functional impairment and for a subscale of 8 of these indicators. For the subscale, additive genes accounted for approximately 21% of covariance in liability for a higher score, whereas unique environment accounted for approximately 7% of variance, with age accounting for a very small proportion. In two indicators there were nontrivial effects of common environment.

Conclusions. Within the expressed limits on generalization, the study findings suggest a major potential role for interventions aimed at a person’s unique environment to maintain good functioning in aging and to lengthen the period of active life. Genetic effects play a modest but also important role in age-related functional impairment.

Efforts to identify and modify the determinants of mortality in later life have expanded in recent years to concerns about the quality of extended life, especially as reflected in functional impairment (1). Issues have centered on the effectiveness of lifestyle health patterns in maintaining elders at their best possible standard of functioning. In this respect, it is important to know the relative influence of inheritance in contrast to other determinants of the life course of functioning. To the extent that genetic constitution is a major force in the outcomes of functioning across the life span, it may leave less room for the ameliorating role of public health, personal initiatives, and service interventions.

Isolating a genetic link to active life is complicated by human genetic heterogeneity, multiplicity of potential nature–nurture permutations, and a wide variety of patterns of aging (2). Because of the complex nature of functioning and the difficulty of designating nonhuman analogs (3), it is not surprising that considerably more is known about genetic relationships with specific health conditions than with functioning in the later years of life. However, the strong correlation of impaired functioning with states of morbidity (3) suggests that informative relationships between genetics and functioning patterns in aging are also likely.

Genetics, in contrast to lifestyle and environmental agents, generally has a relatively minor influence on age-related disorders and health in mammals and invertebrates (4), although there are exceptions. Certain deleterious gene loci have been associated with accelerated changes characteristic of aging. Presenilin 1 and 2 mutations, amyloid precursor protein gene mutations, and the apolipoprotein E e4 (APOE e4) allele increase the risk for Alzheimer’s disease (5–7), coronary artery disease (8), and possibly ischemic cerebrovascular disease (9). APOE e4 is found less frequently in centenarians than in younger adults. Conversely, the e2 allele of APOE, which is associated with a reduced risk for Alzheimer’s disease (10), and the angiotensin-converting enzyme (ACE) DD genotype are both found more frequently in centenarians than in younger adults (11,12).

Genetic influences probably operate mostly through the medium of age-associated diseases. However, Albert and colleagues (13) found that the APOE e4 allele was associated with increased functional impairment even when controlled for comorbid conditions and neuropsychological performance. Possibly there are also nonspecific genetic effects on functional impairment (14–16).

Christensen and colleagues (17) surveyed Danish twins aged 75 years and older (n = 3099) to estimate the heritability of functioning using structural equation analyses. The variation attributable to heritability was 34% to 47% in women 80 years and older but only 15% to 34% for those aged 75 to 79 years. They noted that heritability was low among men, but they did not have sufficient numbers of men in their sample to make precise estimates.

Setting aside birth defects and neonatal complications, much of the incidence and prevalence of functional impairment in the adult population emerges during the later
periods of life, especially during the watershed years of the eighth decade. It is therefore informative to assess the heritability of impairments in functional status of persons passing through their eighth decade who are known to have been healthy at some point in their young adult years. A unique opportunity to do this arose by studying members of the National Academy of Sciences–National Research Council (NAS-NRC) Twin Registry, all of whom were born in the years 1917 to 1927 and who served in the military.

The secondary analyses reported here were designed to evaluate the genetic basis for functional impairment at older ages, using the classical strategies of comparison of monozygotic and dizygotic twin pairs, in a sample of men aged 70 to 80 years. Functional impairment was defined by self-reported reduced mobility, health limitations on performance of desired activities, and the need for assistance in the basic activities of daily living. The hypothesis was that monozygotic twins would be more concordant than dizygotic twins with respect to age-associated functional impairments.

**METHODS**

**Study Participants**

Participants were members of the NAS-NRC Twin Registry, which was constructed by obtaining twin birth certificates for white male births in the years 1917 to 1927 and determining the military service of these twins. A total of 108,000 twin names were collected and matched against the VA Master Index of the Department of Veterans Affairs. This process generated 15,924 twin pairs (31,848 persons) in which both twin pair members had served in the armed forces, mostly in World War II and some in the Korean Conflict. Details of the development and characteristics of the initial twin cohort have been described elsewhere (18).

Methods of establishing zygosity are estimated by cross-validation to be 95% correct (19) as determined in 13,486 twin pairs: Approximately 11,000 assignments of pairs were based on questionnaire data about the twins as children, 1950 on blood typing, and 800 on physical characteristics including fingerprints. Essentially, monozygotes were “alike as two peas in a pod.”

The cohort examined in the current study were participants in the third wave of data collection for a longitudinal study of the epidemiology of Alzheimer’s disease (unpublished data). The third wave sample consisted of 10,456 participants or by proxy informant if the participant could not complete it himself because of cognitive, medical, speech, or hearing disorders.

**Data Collection**

A telephone survey of surviving and consenting twin pairs from the NAS-NRC Twin Registry was carried out from 1996 to 1998. The telephone interview included a measure of cognitive status and questions about occupational history, history of exposure to chemical substances, medical history, medication use, and functional impairment. The telephone interview was completed by the participants or by proxy informants if the participant could not complete it himself because of cognitive, medical, speech, or hearing disorders.

**Functional questionnaire.—**Each participant was asked a brief set of questions about their level of functioning: (a) Blocks Walked Without Rest (blocks): How many city blocks or the equivalent can you walk without a rest? If answer is vague: What distance is that in miles, yards, or feet? Can you walk 10 or more blocks? Rest means stopping or pausing before continuing to walk. (b) Health-Limited Activities (HLA): How does your health affect your daily activities? What things does your health stop you from doing as much as you would like? Leisure activities? Light chores (e.g., dusting, tidying, laundry)? Heavy chores (e.g., washing floors, home repairs, vacuuming)? Holding a paying job? Getting around (e.g., outside the home)? Carrying heavy packages? Traveling around outside the neighborhood? Social activities (e.g., visiting, being visited)? (c) Personal Care Assistance (Assistance): Do you need anyone to regularly assist you in looking after yourself? If the answer is vague: Do you need help in getting out of bed, bathing, dressing, or feeding yourself?

**Biometrics of the functional questionnaire.—**The items for assessing function in this study are drawn from the Comprehensive Assessment and Referral Evaluation (CARE). The CARE covers a wide range of indicators of a person’s potential for achieving a preferred quality of life (20). Its bounded focus is on health and social problems associated with aging, including psychiatric disorders. Originally developed for intensive studies of community-dwelling elders (21), the rater-administered CARE has given rise to both participant and informant versions adapted and used for studies in specific settings (22, 23). The general style of the CARE relies on scripted questions with precoded answers.

Satisfactory reliability, validity, and operational characteristics for discriminating diagnoses of the CARE scales have been established (24–27). Transition tables have shown a range of incidence, chronicity, and recovery from threats to quality of life (28); these also reflect a power to predict specific quality-of-life outcomes. Cross-tabulations reveal that the various domains are sufficiently independent to be usefully measured separately (29).
The time allotted to the assessment of function in the telephone survey required a selection of items rather than the use of whole scales from the CARE. A description of the selected items is given below together with their psychometric properties taken from analyses on the data archives of the North Manhattan Aging Project, which included 2031 participants (30).

Nine of the 10 items are identical to items in the CARE interview. These 9 items are, respectively: (a) Eight items about HLA that constitute a subscale of the Activities Limitation homogeneous scale. The HLA subscale has an alpha coefficient of reliability of .90 and a correlation with the subscale of Instrumental Activities of Daily Living (IADL) (another subscale of the same homogeneous scale) of .678 (p < .001). The HLA subscale is scored from 0 to 8. (b) One item on Blocks Walked Without Rest (Blocks) taken from the Ambulation homogeneous scale. The item responses are recorded as a number ranging from 0 to 10+. A correlation with a hierarchical organized scale of the range of items in the Ambulation homogeneous scale is .75 (p < .001).

The tenth item is newly constructed to summarize information on Personal Care Assistance (Assistance), which previously had been covered by multiple items on assistance in the Instrumental (IADL) and Basic Activities of Daily Living (BADL) subscales of the Activities Limitation homogeneous scale. The nearest comparable item in the North Manhattan Aging Project data is Receipt of Home Assistance, and this item correlates with the IADL scale at .55 (p < .001). All of the 10 selected items are significantly intercorrelated (p < .001). All are also significantly correlated (p < .001) with a validated scale of cognitive impairment (CMSQPR1C), with a range of $X^2$ between .11 and .23.

The analytic strategy is to represent the dependent variable, functional impairment, as a continuum of the HLA subscale, and as dichotomous scores of the Blocks and the Assistance summary items. In addition, each of the 8 HLA items is analyzed in dichotomous form to detect possible differential effects. Although we intended to analyze data on Blocks as a continuous measure, there were significant problems with such an approach. In particular, participants who did not respond with a number to the question “How many blocks can you walk?” were asked whether they could walk 10 blocks or more. This resulted in approximately one third of all responses being the number 10. Therefore, we dichotomized the number of blocks walked into categories 0 to 9 and 10 or more.

Statistical Analysis

We used covariance structural analysis to analyze these data, as implemented in the software package Mx (31), with separate threshold estimates for monozygotic and dizygotic pairs. This type of analysis, which rests on the premise that monozygotic twins share twice as many genes on average as do dizygotic twins, partitions the covariance between twins in a pair into components that are attributable to additive genetics, common environment, and unique environment. Additive genetics are used to estimate heritability, whereas common environment effects are due to such things as shared family upbringing, and unique environment effects are specific to the individual experience. Studies that include a sizable number of twins reared apart can help distinguish additive genetics from common environment effects, but we had too few twin pairs reared apart (only 1% to 2%) for that approach to be useful. It is difficult statistically to distinguish the effects of additive genetics and common environment, both of which tend to increase concordance rates among twins (32), and for this reason we chose to fit ACE (“full”) models to the data rather than to rely on reduced models.

RESULTS

Prevalence

The prevalence rates of functional impairments are slightly and consistently lower in monozygotic than in dizygotic twins, as shown in Table 1. All but three items of functioning (needs assistance, carry heavy packages, getting about) showed a statistically significant difference.

Table 1 also shows proband-wise concordance rates for the presence of problems. In all but one function (needs regular assistance), the concordance rates are higher in monozygotic than in dizygotic twins.

Each of the 10 functions was evaluated separately for variance resulting from additive genetics, common environment, and unique environment (Table 2). For 8 of the 10 indicators of functional impairments, the size of the additive genetics effect ranged from 19% to 33%, but the confidence limits included 0 in all but 3 indicators (carrying heavy packages, leisure activities, and holding a job). Virtually all the remaining variance was attributed to unique environment except in two instances (mobility and regular assistance), in which a small proportion of variance was attributed also to common environment, and in both indicators the confidence limits included 0.

The fit of the ACE model to the 8-item HLA domain produced the following approximate results (with 95% confidence intervals [CI] in parentheses) for covariance in liability for a higher score: additive genes, approximately 21% (95% CI, 14.4% to 27.5%); common environment, approximately 0% (95% CI, 0% to 3.8%); and unique environment, approximately 78% (95% CI, 72.9% to 82.9%). The confidence limits for the 8-item HLA score results are relatively narrow compared with those for individual indicators of functioning and did not include 0 for A or E.

The difference in average age between monozygotic and dizygotic twins is quite small (73.32 for monozygotic, standard error 0.06; 73.41 for dizygotic, standard error 0.06), and the range of ages in our sample is relatively small (spanning only 11 years). Nevertheless, because age has such a potentially strong influence on functional status, we included it in the structural covariance analysis of the 8-item HLA domain to determine how large an effect it had. Age had a very small effect. Covariance in liability for a higher HLA score attributable to age is approximately 1% to 2% (95% CI, 0.8% to 2.2%). Therefore, we did not include it in the analyses of the individual items. The small effect of age is probably a reflection of the limited age range of the twins in our sample.
DISCUSSION

In 8 of the 10 individual item indicators of functional impairments, additive genes accounted for 19% to 33% of covariance in liability for impairment, but the confidence limits included 0 in all but 3 indicators. Unique environment accounted for nearly all the remaining variance in liability to functional impairment, and the confidence limits for all items excluded 0. In a corresponding analysis of a summary score of the 8-item HLA domain, the covariance in liability for a higher score of functional impairment was approximately 21% for additive genetics, with unique environment accounting for approximately 78% of variance, with comparatively narrow confidence limits that did not include 0. The narrowed limits of confidence for the 8-item HLA score results compared with the individual indicators of functioning demonstrates the greater analytic power achieved with the continuous, measured data compared with the categorical data.

The prevalence rates of functional impairments are slightly lower in monozygotic than in dizygotic twins. Because the monozygotic twins are somewhat more concordant than dizygotic twins in functioning, perhaps monozygotic twin pairs with any twin functionally impaired will be more often excluded from the study sample because the other twin has died, compared with the comparable case of dizygotic twins. This study of only intact pairs might thus have favored selection of monozygotic twins with slightly better functioning than that of dizygotic twins. Another possibility is that reciprocal social support between monozygotic twins is greater than it is between dizygotic twins. The proportion of twin pairs who reported meeting “often” was 39% for monozygotic pairs and 25% for dizygotic pairs (unpublished observations).

The absence of analytic evidence of additive genetics in two functions (needs assistance and limitation of light chores) should be viewed with caution because the prevalence rates of those two functions were very low. As this cohort ages, we would expect that those functions will become more frequently limited by health. Other differences between the 10 functions in levels of additive genetic variance are not sufficiently large to warrant explanation unless this pattern of differences is replicated. Nonetheless, we note that the criteria “cannot walk 10 blocks” and “needs regular assistance” have nontrivial effects of common environment, and, for the latter trait, the effects of common environment overwhelm those of additive genetics.

This sample excluded 58 pairs in which both twins were alive and at least 1 member had a diagnosis of dementia from a previous wave of data collection. However, only 15 (26%) of those pairs were concordant for dementia. Although the results reported here cannot be confidently generalized to a population without these exclusions, it seems likely that the additive genetic variance for functional status was not substantially influenced by the selection.

In the sample of Danish twins evaluated by Christensen and colleagues (17), heritability was most marked in women

<table>
<thead>
<tr>
<th>Function</th>
<th>MZ Prevalence (%)</th>
<th>MZ Concordance (%)</th>
<th>DZ Prevalence (%)</th>
<th>DZ Concordance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannot walk 10 blocks</td>
<td>22.5</td>
<td>33.8</td>
<td>26.2</td>
<td>32.5</td>
</tr>
<tr>
<td>Health limitations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy packages</td>
<td>25.6</td>
<td>37.7</td>
<td>27.7</td>
<td>32.9</td>
</tr>
<tr>
<td>Leisure activities</td>
<td>22.7</td>
<td>31.5</td>
<td>25.1</td>
<td>27.2</td>
</tr>
<tr>
<td>Heavy chores</td>
<td>22.1</td>
<td>32.3</td>
<td>25.8</td>
<td>30.7</td>
</tr>
<tr>
<td>Holding a job</td>
<td>15.1</td>
<td>29.8</td>
<td>17.5</td>
<td>23.9</td>
</tr>
<tr>
<td>Getting about</td>
<td>8.1</td>
<td>17.8</td>
<td>9.6</td>
<td>9.3</td>
</tr>
<tr>
<td>Light chores</td>
<td>6.6</td>
<td>10.0</td>
<td>8.1</td>
<td>7.4</td>
</tr>
<tr>
<td>Travel</td>
<td>5.3</td>
<td>12.3</td>
<td>7.5</td>
<td>8</td>
</tr>
<tr>
<td>Social activities</td>
<td>4.3</td>
<td>11.7</td>
<td>6.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Needs regular assistance</td>
<td>2.4</td>
<td>6.0</td>
<td>3.2</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Note: MZ = monozygotic; DZ = dizygotic.

<table>
<thead>
<tr>
<th>Function</th>
<th>Additive Genetics</th>
<th>Common Environment</th>
<th>Unique Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannot walk 10 blocks</td>
<td>27.2 (0–35.3)</td>
<td>4.1 (0–24.6)</td>
<td>73.7 (64.6–83.5)</td>
</tr>
<tr>
<td>Health Limitations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy packages</td>
<td>27.4 (4.4–35.4)</td>
<td>0.1 (0–18.2)</td>
<td>72.5 (64.5–81.2)</td>
</tr>
<tr>
<td>Leisure activities</td>
<td>18.7 (0.4–27.1)</td>
<td>0.1 (0–13.8)</td>
<td>81.5 (72.8–90.3)</td>
</tr>
<tr>
<td>Heavy chores</td>
<td>23.7 (0–32.2)</td>
<td>0.1 (0–20.9)</td>
<td>76.2 (67.7–85.9)</td>
</tr>
<tr>
<td>Holding a job</td>
<td>33.4 (4.9–42.9)</td>
<td>0.1 (0–16.7)</td>
<td>66.5 (57.0–77.1)</td>
</tr>
<tr>
<td>Getting about</td>
<td>21.7 (0–35.1)</td>
<td>0.1 (0–16.7)</td>
<td>78.2 (64.8–92.1)</td>
</tr>
<tr>
<td>Light chores</td>
<td>8.2 (0–24.3)</td>
<td>0.1 (0–16.3)</td>
<td>91.7 (75.6–99.8)</td>
</tr>
<tr>
<td>Travel</td>
<td>19.3 (0–35.9)</td>
<td>0.1 (0–21.6)</td>
<td>80.6 (64.0–98.0)</td>
</tr>
<tr>
<td>Social activities</td>
<td>21.1 (0–39.3)</td>
<td>0.1 (0–23.9)</td>
<td>78.8 (60.6–98.1)</td>
</tr>
<tr>
<td>Needs regular assistance</td>
<td>1.5 (0–46.3)</td>
<td>17.3 (0–37.5)</td>
<td>81.2 (53.6–99.8)</td>
</tr>
</tbody>
</table>

Note: 95% confidence intervals in parenthesis.
ACKNOWLEDGMENTS

The opinions and assertions contained herein are those of the authors and are not to be construed as reflecting the views or positions of the National Academy of Sciences, the Institute of Medicine, or the National Research Council.

The data for this study were abstracted from a longitudinal study of the epidemiology of Alzheimer’s disease: Drs. John Breitner and Brenda Plassman, Principal Investigators (NIA AG-08549).

Address correspondence to Barry J. Gurland, MD, Columbia University Stroud Center, Tower 3, Apt. 30F, 100 Haven Ave., New York, NY 10032.
E-mail: bg1@columbia.edu

REFERENCES


Received September 18, 2002
Accepted May 14, 2003