REPORT FROM THE CRITICAL EVALUATION STUDY COMMITTEE OF THE COGNITIVE AND EMOTIONAL HEALTH PROJECT

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Report from the Critical Evaluation Study Committee of the Cognitive and Emotional Health Project

Preamble

Three Institutes, the National Institute on Aging, the National Institute of Mental Health and the National Institute of Neurological Disorders and Stroke, joined efforts to launch a new trans-NIH initiative, The Cognitive and Emotional Health Project (CEHP). This project seeks to identify the demographic, social and biologic determinants of cognitive and emotional health in the older adult. Identifying the factors that can help people maintain or enhance their cognitive and emotional health as they grow older would have significant public health implications for the ever-burgeoning population of older adults in the United States. Staff from the National Institute on Aging (Dr. Molly Wagster), the National Institute of Mental Health (Dr. Bruce Cuthbert) and the National Institute of Neurological Disorders and Stroke (Dr. Emmeline Edwards) currently coordinate the effort.

Several activities to determine the state of knowledge in this area and to determine where further research is needed have been undertaken by the tri-Institute task force, including a workshop held in July 2001 entitled, "Cognitive and Emotional Health: The Healthy Brain Workshop." A description of these activities is included in the website http://trans.nih.gov/CEHP/ .

In response to the original goals of the Project and also to the recommendations from this workshop, a committee of extramural and intramural research scientists was established in September 2003 to conduct a critical analysis of the existing scientific literature pertaining to factors involved in the maintenance of cognitive and emotional health. Based upon this analysis, the goal of the committee was to outline the strengths as well as weaknesses in the current knowledge of these factors and to make recommendations for future research opportunities - for example, recommending and prioritizing ancillary or secondary data analytic studies, adding new measures to existing studies that could help fill in the gaps in our knowledge. The members of the Critical Evaluation Study Committee were: Dr. Marilyn Albert (Johns Hopkins University), Dr. Meryl Butters (University of Pittsburgh), Dr. Sujuan Gao (Indiana University), Dr. David Knopman (Mayo Clinic), Dr. Lenore Launer (National Institute on Aging Intramural Research Program), Dr. Kristine Yaffe (University of California at San Francisco), and Dr. Hugh Hendrie (Indiana University) [chair]. Drs. Cuthbert, Edwards, and Wagster served as *ex officio* members. The committee organized its efforts through a series of face-to-face meetings, monthly telephone conference calls and email correspondence to discuss issues relevant to this charge and to implement the comprehensive study.

Introduction

At the 2001 meeting of 'Cognitive and Emotional Health: The Healthy Brain Workshop', which preceded the formation of the critical analysis task force, definitions of what constitutes cognitive and emotional health were discussed. It was proposed that cognitive health as it pertains to the elderly should be defined not just as the absence of disease, but rather as the development and preservation of the multidimensional cognitive structure that allows the elderly to maintain social connectedness, an ongoing sense of purpose,

and the abilities to function independently, to permit functional recovery from illness or injury and to cope with residual functional deficits.

A major component of many observational studies in this field of research is identifying factors that preserve cognitive function or prevent cognitive decline. While risk factors for the major dementing disorders such as Alzheimer's disease (AD) will certainly be risk factors also for cognitive decline, it is conceivable that risk factors not specifically associated with AD or other dementing disorders may be identified as factors for cognitive decline. For example, there are other common age related non-AD pathophysiological processes which could produce cognitive decline or cognitive impairment either singly or collectively, including milder forms of cerebrovascular disease and cell loss due to oxidative stress, inflammation, or apoptosis. Studies of cognitive decline might therefore identify a different set of risk factors both genetic and environmental (or possibly place different weights on known risk factors) than would studies of single dementing disorders. Many of these processes may be preventable (The Aging Mind 2000). Some cognitive processes decline almost inevitably even in healthy older adults. This has been attributed to "normal" aging. However, past experience with geriatric research should leave room for skepticism about attribution of any functional decline to "normal" processes.

Significant cognitive decline is very common in the elderly population (Unverzagt et al. 2001). Individuals with cognitive decline are at much greater risk for developing dementing disorders. Thus, identification and early treatment of these individuals might prove to be a very effective strategy for preventing dementia. Cognitive reserve has been proposed as a mechanism to explain why some individuals may not exhibit the clinical manifestations of dementia while other individuals do with the same load of brain pathology (Scarmeas and Stern 2004). Cognitive reserve as measured, for example, by general intelligence, has been associated with higher occupational attainment and education, as well as increased participation in intellectual, social, and physical activities. This suggests implementing alternative or complementary strategies for reducing risk for dementia.

Studies of healthy brain aging, such as the MacArthur Study of Healthy Aging (Rowe and Kahn 1998), have been much less common than studies of cognitive decline. Results from these studies have suggested that "successful" aging should be distinguished from "normal" aging. They have also tended to emphasize psychosocial factors as major influences in maintaining cognitive health and have suggested appropriate prevention strategies involving lifestyle changes. One ongoing intervention trial, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE), has demonstrated that some cognitive processes such as speed of processing and reasoning ability, can be enhanced at least temporarily in the elderly by intellectual exercises (Ball et al. 2002). This article stimulated an editorial from Christine Casel entitled, "Use it or Lose it. Activity may be the best treatment for the physical and functional declines associated with aging" (Casel 2002). Perhaps successful cognitive and emotional aging has been so little studied because it represents a concept that is truly novel to humanity in the late 20th century and into the 21st century. Expectations for healthy cognitive aging may currently be too restrictive, based as they are on a survival cohort of hardy individuals who overcame great odds to reach the eighth decade of life or beyond. As we look into the

21st century and the prospects of elders with a much broader range of physiological and psychosocial functioning surviving into these age groups increase, these expectations may well change.

Similarly, 2001 workshop participants concluded that emotional health is not just the absence of psychiatric illness or even the absence of negative affect that in certain contexts can be constructive. Rather, it should be defined more comprehensively, including constructs such as emotional regulation and emotional intelligence. Emotional regulation refers to the ability of individuals to control their emotion, whereas emotional intelligence refers to the ability of the individual to use and identify emotions constructively. Studies of emotional health in the elderly have identified individual characteristics that promote successful adaptation, variously described as resilience, mastery, self-efficacy, or emotional vitality. Baltes and Baltes, in their Berlin Aging Studies, have proposed that successful adaptation in the elderly involves processes of selection, optimization and compensation and that some fortunate elderly, as a result of their life experiences, develop "wisdom," which is defined as the ability to exercise good judgment about important but uncertain matters in life (Baltes and Baltes 1990). Blazer has suggested that strengthening self-efficacy, the ability to engage self and the environment to facilitate functioning and social opportunity in those many elderly individuals who express feelings of sadness and loneliness, might be a successful prevention strategy for psychiatric disorders for these vulnerable people (Blazer 2002). Self-efficacy and its synonyms are often considered a relatively enduring character trait. However, one of the few studies that analyzed emotional vitality as an outcome reported that it was also influenced by health status, disability and other sociodemographic factors which suggests a more complex relationship between this trait and the sociodemographic context (Penninx et al. 1998). Studies that are longitudinal in design could help to disentangle the direction of this relationship. It is also likely that, as the concept of emotional health becomes the focus for ongoing research, it will need to be broadened beyond those mentioned in this report. Carstensen and her colleagues, for example, in their theory of socio-emotional selectivity have suggested that as part of the aging process, individual goals become more present oriented and related to emotional meaning rather than future oriented and related to acquiring new information or new experiences. This age related motivational change exerts a major influence on social preferences, maintenance of social networks and emotional regulation, as well as cognitive processing (Lockenhoff and Carstensen 2004).

Emotional health and cognitive health are often considered separately in research studies, as are psychiatric disorders and dementing disorders. At least two recent NIH-sponsored reports have expressed concern that this separation has created problems in developing appropriate research and treatment strategies in the elderly where emotional and cognitive problems are common and interactive (Steffens et al. 2006; NAMHC 2003). Both reports suggested more comprehensive approaches to the disorders of the elderly involving collaborations across NIH Institutes. The 2001 workshop participants also concluded that consideration of emotional health separate from cognitive health is impossible as emotion is always involved in cognitive processes. Three biological processes have been identified to explain the interaction of cognition and emotion: gluco-corticoid secretion, brain derived neurotrophic factor regulation of synaptic activity (both

stress related) (Heuser and Lammers 2003), and cerebrovascular disease which may be a risk factor for both cognitive impairment and depression (Alexopoulos et al. 2000).

There has been considerable interest recently in health promotion strategies in neurological disorders as well as in other medical fields. Two national organizations have recently launched health promotion campaigns focusing on cognitive health, the American Association of Retired People with their "Staying Sharp" project and the Alzheimer's Association with the "Maintain Your Brain" campaign. The Alzheimer's Association campaign was based not only upon the growing evidence linking lifestyle factors such as diet and exercise with AD risk, but also on the assumption that a campaign promoting brain health is likely to attract a younger and more diverse audience than one focused simply on a disease of the elderly. Thus, the impact of the proposed prevention strategies might have a greater and wider impact in the population at large. This parallels approaches in other health disciplines. For example, the Healthy People 2000 report from the Public Health Service of the Department of Health and Human Services (DHHS) is subtitled 'National Health Promotion and Disease Prevention,' suggesting that the two goals of disease prevention and health promotion are complimentary. It is also probable that the guidelines for healthy individuals to maintain health may be different than those recommendations for at risk subjects to prevent disease.

The 2001 workshop participants concluded that an NIH trans-Institute initiative focusing on cognitive and emotional health and their interactions was both pertinent and timely, and that large cohort longitudinal studies might be an ideal vehicle to affect this. They also recommended that a committee be formed to conduct a critical analysis of existing studies prior to making specific recommendations.

The remainder of the report describes the findings and suggestions of the Critical Evaluation Study Committee.

The Critical Evaluation

Criteria for Cognitive and Emotional Health

The initial discussions of the committee concentrated not only on identifying criteria for cognitive and emotional health, particularly as they apply to the older adult, but also how these criteria could be operationalized and applied to the existing published data. Ideally, assessments of cognitive function should involve measurements of multiple cognitive domains: memory, spatial orientation, learning, executive functions, and language. These measurements should not have ceiling effects that limit sensitivity, particularly with longitudinal measurements Assessments of emotional health should include not only absence of major psychiatric disorders but, evidence of positive affect, as exemplified in quality of life and life satisfaction scales, as well as evidence of such characteristics as resilience, hardiness, and emotional vitality. This approach is based upon the presumption that some of these characteristics comprise strong protective factors against many of the disorders and illnesses associated with the elderly.

In order to address the concept of the preservation and promotion of cognitive and emotional health, the committee decided to focus its review on cognitive outcomes such as cognitive performance and cognitive decline, rather than clinically defined outcomes, such as dementia, mild cognitive impairment, and AD. For emotional outcomes, the

committee would review the presence of depressive symptoms, anxiety symptoms, positive and negative affect, mastery, and resilience rather than the clinical syndromes, Major Depressive Disorders, Anxiety Disorders, etc.

Criteria for studies to include in the critical evaluation

Because a major goal of the Cognitive and Emotional Health Project was to "assess the state of longitudinal and epidemiological research on demographic, social, and biological determinants of cognitive and emotional health among adults, to determine how these pathways reciprocally influence each other…", the committee decided to concentrate on those studies that were observational or interventional, large cohort, predominantly with participants 65 years or over, and studied a broad range of demographic, biological, and psychosocial risk factors. A somewhat arbitrary sample size of greater than 500 was selected to meet these goals. In epidemiological studies a longitudinal design confers considerable advantages in determining causation over cross-sectional studies involving a single outcome measurement. However, the committee did make two exceptions to the criteria for longitudinal design. Due to concern that there may be few studies with emotional outcomes involving multiple measurements over time, cross-sectional studies for emotional outcomes were included. An exception was also made for cognitive outcome studies where biological data was gathered some years previously in the setting of an ongoing cohort study, and subsequently, cognitive assessments were added (so-called piggy back studies).

The committee next reviewed the data that were generated from a questionnaire sent to principal investigators of epidemiological and other large cohort studies supported by NIH to determine whether or not it was feasible to operationalize these "ideal" criteria. Questionnaire responses from a total of 80 studies have been recorded in a Web-based database maintained at the NIH (see http://trans.nih.gov/CEHP/hbq/search.asp). Many studies did include some measurements of the important domains of cognitive and emotional health that might yield useful information, but they were not sufficient to meet the committee's "ideal" criteria. Therefore, to incorporate as many of these studies as possible, it was decided to modify and simplify the inclusion criteria for the critical analyses.

To summarize, the final criteria for inclusion into the analyses on cognitive and emotional outcomes were the following:

- Sample size > 500
- Age predominantly 65 and over
- Longitudinal in design
    - ✓ At least one follow up evaluation of cognitive function, or
    - ✓ Single evaluation of cognitive function with exposure measured a certain year prior to cognitive function
- Measurement of memory and at least one other cognitive domain
- Measurement of depression symptoms and at least one other domain such as quality of life, sense of control, self-efficacy, resilience, hopelessness or optimism

- For emotional outcomes, cross-sectional studies were also included.

These criteria were then applied to the database of questionnaire responses, yielding a total of 27 studies that met these criteria. Because of its major focus on emotional outcomes, the Established Populations for Epidemiological Studies of the Elderly (EPESE) was also added, although the study was not included in the database.

Members of the committee were also aware of the fact that there were a number of large existing international studies not supported by NIH that could yield very important information on cognitive and emotional health. It was decided, therefore, to incorporate some major European and North American studies into the analysis. The studies included in the analyses were: Medical Research Council Cognitive Function and Aging Study, Berlin Aging Study, Rotterdam Study, Personnes Agees Quid Study, Swiss Interdisciplinary Longitudinal Study, Longitudinal Aging Study Amsterdam, Kungsholmen Project, and Amsterdam Study of the Elderly. Table 1 shows all of these 36 North American and European studies included with this report.

A bibliographic search for publications pertaining to the identified studies was conducted using PubMed supplemented by Ovid/PsycINFO; 1880 articles were identified. Abstracts from these articles were sent to the committee members for a preliminary review to determine whether or not they met criteria for inclusion in the evaluation. From this preliminary review, 266 abstracts were selected for full text review. (Full texts of these articles are available upon request.) The texts were reviewed by a doctoral candidate from Indiana University, Sven Klingeman, with the assistance of Drs. Gao and Hendrie. Of these 266, 96 articles (66 with cognitive outcomes and 30 with emotional outcomes) from 26 studies met our criteria for further analysis. As a further check on reliability, selected articles were independently reviewed by other committee members. Questionnaire forms and a database were created by Dr. Gao to execute the critical evaluation. These forms were utilized to enter experimental details and findings from the published reports of these selected studies. In addition to providing pre-selected risk factor categories, the forms contained a provision for write-ins. The entered data is available for review on the website: http://www.biostat.iupui.edu/~sgao/healthybrain/hblogin.asp, although minor changes were made as part of the survey process. Figure 1 illustrates the selection and review process that was used.

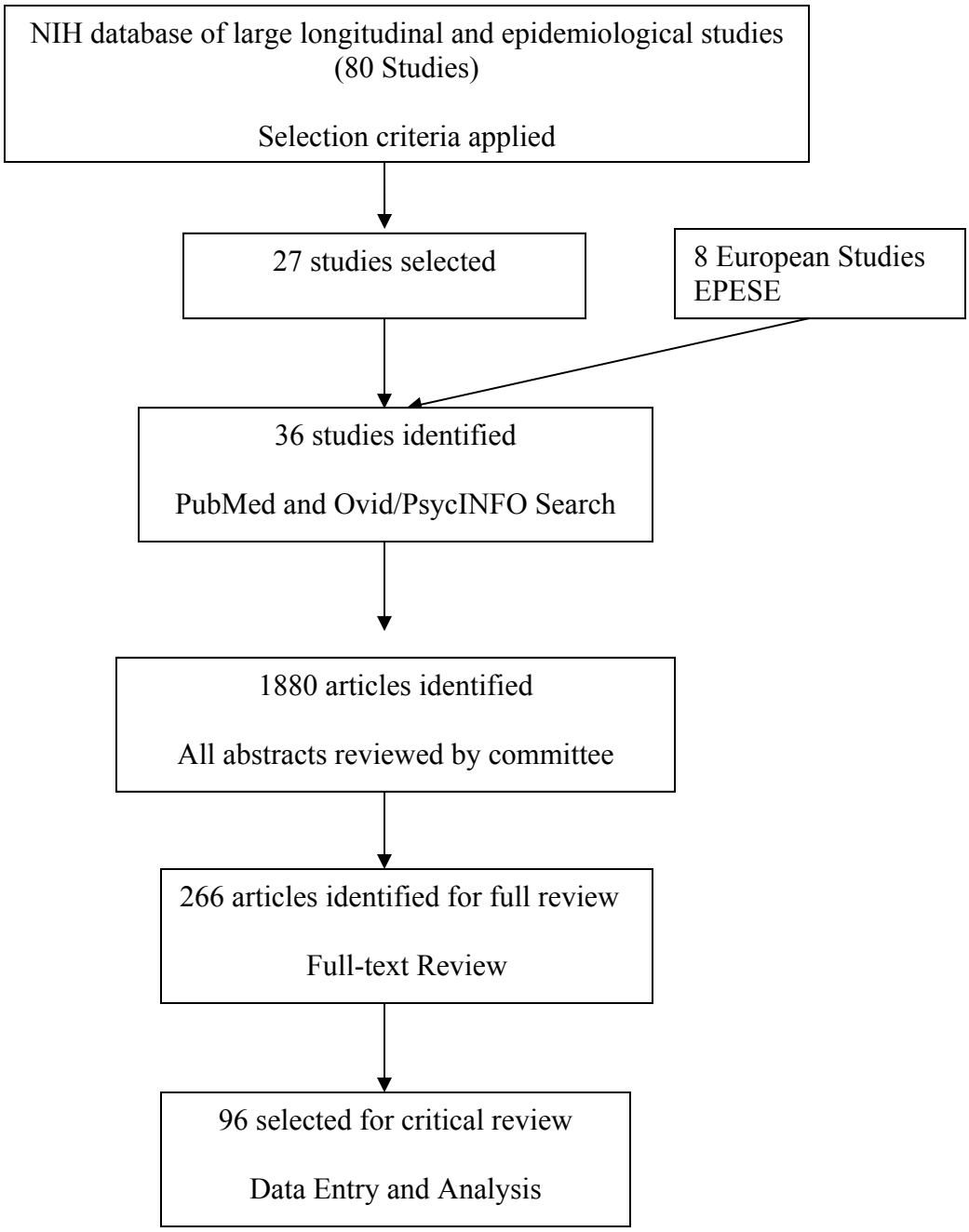
Studies Included in the Critical Evaluation

Table 1. Studies included in the critical evaluation

#	**Principal Investigator**	**Title of Study**
1	Baltes, P.B.	Berlin Aging Study
2	Blazer, Dan et al	Established Populations for Epidemiological Studies of the Elderly (EPESE)
3	Brayne, Carol & Huppert, Felicia	Medical Research Council Cognitive Function and Aging (MRC CFA) Study
4	Breitner, John	Epidemiology of Dementia in Cache Co., Utah
5	Breteler, M.M & Hofman, A	Rotterdam Study
6	Cummings, Steve	Study of Osteoporotic Fractures [SOF]
7	Dartigue, Jean Francis	Personnes Agees Quid [PAQUID]
8	Evans, Denis	Chicago Health and Aging Project [CHAP]
9	Guilley, Edith; Armi, Franca; Ghisletta, P.; Bickel, Jean-François	Swiss Interdisciplinary Longitudinal Study on the Oldest Old (SWILSO-O)
10	Grodstein, Francine	Trials of Prevention of Cognitive Decline in Women and Men (Ancillary of Women's Health Study)
11	Grodstein, Francine	Trials of Prevention of Cognitive Decline in Women and Men (Ancillary of Physicians' Health Study)
12	Grodstein, Francine	Trials of Prevention of Cognitive Decline in Women and Men (Ancillary of Women's Antioxidant Cardiovascular Study)
13	Grodstein, Francine	Preventing Cognitive Decline- A prospective Study (Ancillary of Nurses' Health Study)
14	Harris, Tamara	Health Aging and Body Composition (Health ABC) Study
15	Hauser, Robert	Wisconsin Longitudinal Study (WLS)
16	Jonker, C	Amsterdam Study of the Elderly (AMSTEL)
17	Jonker, C.	Longitudinal Aging Study Amsterdam (LASA)
18	Kuller, Lew	Cognitive tests, APOE, brain MRI and risks of dementia
19	Larson, Eric	KAME
20	Larson, Eric	University of Washington Adult Changes in Thought (ACT) Study
21	Lindsay, Joan & McDowell, Ian	Canadian Study of Health and Aging
22	Mayeux, Richard	The Epidemiology of Dementia in an Urban Community
23	McCann, Judith	Longitudinal Study of Daycare in Alzheimer's Disease
24	Pedersen, Nancy	Swedish Adoption/Twin Study of Aging (SATSA)
25	Pedersen, Nancy	Genetic and Environmental Influences- Biobehavioral Aging
26	Sacco, Ralph	Northern Manhattan Study
27	Schwartz, Brain & Glass, Thomas	Baltimore Memory Study
28	Rowe John	MacArthur Study of Successful Aging
29	White, Lon	Honolulu Asia Aging Study (HAAS) - Honolulu Heart Program
30	Willis, Robert	Health and Retirement Study (HRS)
31	Willis, Robert	Asset and Health Dynamics Among the Oldest Old (AHEAD)
32	Winblad, B. & Fratiglioni, L.	Kungsholmen Project
33	Wolf, Philip	Epidemiology of Dementia
34	Wolf, Philip	MRI, Genetic & Cognitive Precursors of AD & Dementia
35	Wolf, Philip	Precursors of Stroke Incidence and Prognosis, Framingham Heart Study
36	Zelinski, Elizabeth	Longitudinal Study of Cognition in Adults

Review Process

Figure 1: Selection and Review Process



Construction of the Summary Tables

To summarize the extensive literature review captured in the database into relatively simple tables, the committee condensed the review results on three levels. First, it was decided that each study be represented by a single article for each risk factor included in the review. The article selected would be the most recent published article of that study reporting a significant finding for that risk factor. Because many of the studies had multiple articles in the database on the same outcome, this decision ensured that the findings reflected the overall results of the studies and was not biased by multiple reporting from a single study on a given outcome or risk factor. Separate tables were constructed for cognitive and emotional outcomes.

The second level of condensation occurred when a single article in the cognitive section reported on multiple cognitive outcomes (e.g. memory function, language, global cognitive scores, etc.) In the cognitive table, the committee chose to report only the significant findings. For example, a factor could be reported as having no significant association with language yet a significant risk for memory. The significant risk for memory would be included in the cognitive outcome table but the non-significant relationship with language would not.

The third level of data condensation was to combine the many factors captured in the review into fewer factor categories. A large number of factors (439) were included in our original database. To make the tables concise, these factors were grouped together as far as possible into factors with common themes. This was difficult to accomplish in all circumstances, but eventually the list was narrowed to 64 risk factors. The directions of the significant factors were then reviewed so that in the table they were all reported in the same direction (e.g. emotional support factor was redirected to indicate that more emotional support is protective). The result of this grouping process, while making the tables more readable, does result in a loss of information and understates the complexities of some of the relationships. (The factor groupings are included in the appendix.)

For both tables, cross-sectional and longitudinal findings were combined. The table on emotional outcomes incorporates articles reporting on anxiety, depression, dysphoria, negative affect, loneliness, etc. It was difficult to include in the emotional outcome table the few articles that reported on positive outcomes like positive affect, subjective well-being, mastery, or self efficacy. The results from these articles will be described separately in the text.

Summary of Results

The literature review for cognitive and emotional outcomes is presented in Tables 2 and 3.

Table 2. Variables Examined as Predictors of Cognitive Outcomes

Factor	Total Number of Studies[A]	Significant Risk[B]	Significantly Protective[B]	No Significant Association[B]	Adjusted For[C]	Reference Numbers in Survey Bibliography
Age	20	6	0	1	13	4,16,24,27,37,38,44,48,52,57,61,64,66,70,75,85,88,94,95,96
Alcohol	9	0	2	0	7	26,27,32,58,64,70,75,91,95
Alcoholism	1	1	0	0	0	32
Antihypertensive Medication	3	0	0	0	3	23,44,67
Aspirin	3	0	1	1	1	48,50,94
BMI	7	3	0	0	4	3,24,27,58,59,70,95
Baseline Cognitive Function	3	0	2	0	1	18,37,72
Being Married	1	0	0	1	0	77
Biological Factors Inflammation	1	1	0	0	0	95
Brain Imaging --- Infarct/White Matter Lesions	2	2	0	0	0	52,85
Brain Imaging Atrophy	1	1	0	0	0	52
Chronic Disease: Arthritis	2	0	0	0	2	27,48
Chronic Disease: Cancer	1	1	0	0	0	27
Chronic Disease: Osteoporosis	2	1	0	0	1	27,59
Diabetes	8	3	0	1	4	24,27,39,45,48,58,70,94
Diet	1	0	0	1	0	64
Education	20	0	8	1	11	4,16,24,27,34,37,38,44,52,58,61,64,66,70,73,85,88,94,95,96
Female	13	1	0	4	8	2,5,14,33,37,38,44,45,66,72,85,88,95
Functional/Physical disability	4	1	0	1	2	1,27,59,76
Genetic Factors	11	6	0	3	2	5,14,22,27,29,37,78,88,89,92,96
Health	5	0	0	0	5	7,63,75,93,95

Factor	Total Number of Studies[A]	Significant Risk[B]	Significantly Protective[B]	No Significant Association[B]	Adjusted For[C]	Reference Numbers in Survey Bibliography
Heart Disease	10	1	0	3	6	7,26,44,45,48,57,69,70,78,93
Homocysteine	1	0	0	1	0	49
Hormones	5	2	2	1	0	27,40,61,70,71
Hyperlipidemia	4	1	0	1	2	21,24,58,94
Hypertension	9	5	0	0	4	24,36,44,45,55,57,64,70,93
Interaction Genetic	4	2	0	2	0	21,67,78,92
Lead Exposure	1	1	0	0	0	75
Lung	2	0	2	0	0	4,16
Memory Complaints	1	1	0	0	0	22
Menopause	3	0	1	0	2	58,63,71
Mental Health	1	0	0	0	1	57
Mood (low)	5	2	0	0	3	18,27,29,77,91
Multiple Chronic Diseases	4	0	0	0	4	18,27,77,95
NSAIDS (Exclude Aspirin)	4	0	1	2	1	48,50,72,95
Other	4	0	1	1	2	27,38,43,70
Physical Activity	4	0	3	0	1	4,7,16,93
Poor Sleep	1	1	0	0	0	29
Psychosocial Factors: Cultural	2	0	2	0	0	16,37
Psychosocial Factors: Emotional Support/Social Networks	3	0	2	1	0	1,7,77
Psychosocial Factors: Other	1	0	0	1	0	1
Psychosocial Factors: Personality	2	0	1	0	1	57,76
Psychosocial Factors: Stress	1	1	0	0	0	57

Factor	Total Number of Studies[A]	Significant Risk[B]	Significantly Protective[B]	No Significant Association[B]	Adjusted For[C]	Reference Numbers in Survey Bibliography
Psychotropics	2	0	0	0	2	27,57
Race	6	2	0	1	3	4,27,52,64,70,95
Residence	2	0	0	0	2	3,66
SES	8	0	3	1	4	16,24,37,56,63,70,77,86
Sensory Handicap	3	0	0	1	2	7,33,39
Smoking	11	2	0	1	8	24,27,31,38,58,59,64,66,70,75,95
Stroke / TIA	7	3	0	1	3	21,44,45,59,66,69,72
Thyroid	1	0	0	0	1	27
Vitamins	3	0	2	0	1	42,60,64

A: the number of studies that included the factor in their analyses;
B: indicates a significant association and its direction;
C: indicates that the factor was adjusted for in determining the final risk model but, that the direction of the association was not provided.

Table 3. Variables examined as Predictors of Emotional Outcomes

Factor	Total Number of Studies[A]	Significant Risk[B]	Significantly Protective[B]	No Significant Association[B]	Adjusted For[C]	Reference Numbers in Survey Bibliography
Age	8	2	2	1	3	11,30,51,53,65,68,74,83
Alcohol	2	0	0	1	1	62,79
BMI	2	0	0	0	2	68,83
Baseline Cognitive Function	3	0	2	0	1	12,65,80
Being Married	7	1	2	2	2	9,12,30,47,62,65,74
Biological Factors	2	1	0	1	0	20,79
Biological Factors: Inflammation	3	2	0	1	0	20,68,82
Chronic Disease: Gynecological	1	0	0	0	1	87
Chronic Disease: Arthritis	2	1	0	1	0	10,65
Chronic Disease Cancer	1	1	0	0	0	10
Chronic Disease: Lung	1	1	0	0	0	10
Chronic Disease: Other	2	1	0	0	1	51,74
Cognitive Factors: Cognitive Change	1	0	0	0	1	8
Cognitive Factors: Cognitive Function	8	1	3	0	4	9,15,30,47,65,74,83,87
Diabetes	3	2	0	0	1	51,65,83
Education	8	0	4	2	2	12,15,30,47,51,65,74,83
Family History	2	0	0	0	2	8,74
Family Size	1	0	0	1	0	15
Female	7	3	0	1	3	6,12,30,51,68,74,83
Functional/Physical disability	9	7	0	0	2	6,9,30,46,62,65,74,82,87
Genetic Factors	1	0	0	1	0	12
Health	7	0	3	2	2	19,28,30,46,65,79,87

Factor	Total Number of Studies[A]	Significant Risk[B]	Significantly Protective[B]	No Significant Association[B]	Adjusted For[C]	Reference Numbers in Survey Bibliography
Heart Disease	3	3	0	0	0	10,65,81
Homocysteine	1	0	0	1	0	79
Hormones	1	0	1	0	0	87
Hyperlipidemia	2	0	0	1	1	12,83
Hypertension	2	1	0	1	0	62,80
Mental Health	1	1	0	0	0	74
Mood (low)	5	4	0	0	1	12,15,30,65,74
Multiple Chronic Diseases	7	5	0	2	0	10,15,30,46,47,62,74
Poor Sleep	1	1	0	0	0	62
Psychosocial Factors: Childhood	1	0	0	0	1	8
Psychosocial Factors: Cog factors Interaction	1	1	0	0	0	84
Psychosocial Factors: Emotional Support/Social Networks	8	0	6	1	1	30,46,47,51,62,65,74,87
Psychosocial Factors: Other	3	2	0	1	0	15,30,84
Psychosocial Factors: Personality	3	3	0	0	0	9,47,62
Psychosocial Factors: Religion	1	0	0	1	0	30
Psychosocial Factors: Stress	6	5	0	0	1	19,28,30,35,62,74
Psychotropics	4	1	0	0	3	46,68,83,87
Race	3	1	1	1	0	12,30,62
Residence	4	0	1	1	2	6,15,51,68
SES	3	0	2	1	0	11,15,65
Sensory Handicap	3	2	0	1	0	51,62,65
Smoking	3	0	0	0	3	68,83,87

Factor	Total Number of Studies[A]	Significant Risk[B]	Significantly Protective[B]	No Significant Association[B]	Adjusted For[C]	Reference Numbers in Survey Bibliography
Stroke / TIA	2	0	0	1	1	10,82
Vitamins	1	0	0	1	0	79

A: the number of studies that included the factor in their analyses;
B: indicates a significant association and its direction;
C: indicates that the factor was adjusted for in determining the final risk model but, that the direction of the association was not provided.

In both tables 2 and 3, the first column describes the grouped factors. The second column indicates the number of studies that included the factor in their analyses. The third, fourth, and fifth columns indicate the direction of the associations when significant associations between the risk factor and the outcome were determined. The sixth column indicates that the factor was adjusted for in determining the final risk model but, that the direction of the association of the adjusted factor was not provided in the article. The best interpretation of this column is likely that the researchers did indeed find a significant association between the adjusted factor and the outcome in previous analysis, or that they assumed an association based upon prior reports. Thus, for example, adjusting for age in studies with cognitive outcomes is based upon the voluminous literature indicating that increasing age is associated with cognitive decline. The last column includes the reference numbers for all articles included in the second column (see Survey Bibliography).

There was a very wide range of risk factors (64) studied for both cognitive (52 factors) and emotional outcomes (46 factors) with considerable overlap between them. All studies in the survey included age and education in their models to control for potential confounding factors. Studies reporting on specific risk factors typically controlled for potential confounders implicated in previous research findings. For example, most articles reporting on the association between hypertension and cognitive decline controlled for the effect of alcohol, smoking, and Body Mass Index. Details on variables adjusted for in each paper were captured in our database and not presented in the summary tables.

For cognition, the factors most consistently associated with poor outcomes include: increasing age, hypertension, diabetes, stroke or transient ischemic attacks (TIAs), the presence of infarcts or white matter lesions in brain imaging, low mood and higher BMI ratings. The protective factors most consistently reported include higher education levels, higher socioeconomic status (SES), emotional support, better baseline cognitive function, better lung capacity, more physical exercise, moderate alcohol use and use of vitamin supplements.

More inconsistent findings were reported for the possession of the Apolipoprotein E (ApoE) ε4 allele, hormone replacement therapies, and heart disease (this latter finding being perhaps because the results grouped together different measures).

Factors significantly associated with cognitive outcomes in single studies include: biological markers of inflammation, exposure to lead, alcoholism, poor sleep, cancer, osteoporosis (all increasing risk for poor outcomes) and the personality characteristic of mastery, which is protective.

For emotion, the factors most consistently associated with poor outcomes include: functional/physical disability, the presence of chronic illnesses, sensory handicaps, stress, being female, and personality characteristics such as neuroticism, and biological markers of inflammation. Protective factors most consistently reported include higher education, higher SES, good health, better cognitive function, and good emotional support systems.

Inconsistent findings were reported for increasing age and race.

Factors significantly associated with emotional outcomes in single studies included poor sleep, increasing risk, and hormone replacement therapy as being protective. The possession of the ApoE ε4 allele was not significantly associated with emotional outcomes in a single study.

There were 7 articles in both cognitive and emotional outcomes tables describing the results of interactions between risk factors. Four of these analyzed the interactions between ApoE ε4 and other risk factors. They reported that estrogen was associated with less cognitive decline among ε4 negative but not ε4 positive women; ε4 carriers with atherosclerosis were at greater risk for cognitive decline than carriers without ε4; midlife high systolic blood pressure had a stronger adverse effect on cognitive function in persons with ε4, but this effect may be modified by antihypertensive medication: Stroke and ApoE ε4 may impair cognition through non-synergistic mechanisms. Two articles discussed interactions involving educational levels. They reported that depression increased the risk for cognitive decline only on individuals with higher levels of education and formal education accounted for the apparent significant protective effect of current oral estrogen replacement therapy for cognitive decline in older women. One article reported that interactions between neuroticism, loneliness and life events increased the risk of developing anxiety symptoms in older women.

Two studies not included in either Table 2 or 3 examined mastery and/or resilience as outcomes.[17, 51] Major factors associated with poor outcome in this domain were poor health and poor functional ability. Good outcome was associated with family support. Increasing age and being female was associated with poorer outcomes in one study. Four studies considered positive affect or subjective well-being as outcomes. [13, 47, 53, 54] Good subjective well-being was associated with higher SES, whereas poor well-being was associated with functional and physical limitations. The possession of an ApoE ε4 allele had no association with well-being. Extraversion and general intelligence were the strongest predictors of positive affect. Age had no significant effect after controlling for demographic, health, personality and functional capacity.

Discussion

The studies included in this report have large cohorts with complex designs and analyses involving multiple factors and outcomes. The purpose of the review was to determine the nature and extent of the information contained in these large scale studies with regard to factors that are associated with cognitive and emotional health. The results presented in this report are a descriptive summary of the results from these studies as they pertain to these outcomes. The review was not intended to represent a systematic meta-analysis of predictors of cognitive or emotional health. Some major studies which contain much information on these outcomes (e.g., The Seattle Longitudinal Study, Hispanic EPESE study, studies from countries other than North America or Europe) and studies with smaller cohort sizes (<500) were not included in the final analysis for a variety of reasons, thus limiting the scope of our findings. Nevertheless, the analysis does demonstrate the large amount of published information currently available on risk factors for cognitive and emotional outcomes and perhaps, more importantly, the even larger amounts of information on these risk factors which have not yet been published raise the possibility of publication bias (i.e. studies with positive findings are more likely to be reported). For example, all 36 studies were selected because they contained information

on both cognition and emotion, and all contained a broad range of biological and psychosocial variables. Of studies meeting our criteria, we have identified 21 so far who had reported on cognitive outcomes and 12 who reported on emotional outcomes. It is likely in fact that all 80 studies recorded in the database maintained at NIH contain very useful information to explore risk factors for cognitive and emotional health. There were fewer studies in this review that had as the major focus *positive* cognitive and emotional outcomes (for example, the MacArthur Study on Health and Aging and the Berlin Aging Study), but it would also appear that most of these studies would have the capacity to conduct such analyses from their database. The reason for the relatively fewer number of published papers on these outcomes from this group of very productive investigators is likely that the primary focus of most of these studies were disease-oriented (involving, for example, dementia, AD, Major Depressive Disorder) so that analyses on non-disease outcomes were a lower priority. This disease-oriented focus represents the current priorities of the NIH.

The grouping process, both for outcomes and risk factors conducted for reasons of conciseness, also resulted in a loss of information and understates the complexities of some of the relationships. It should also be noted that individual risk factors reviewed here were not necessarily defined by the same criteria and their reported association with cognitive or emotional outcomes may not have all controlled for the same set of covariates. Increasing age was associated with poorer cognitive performance as measured primarily by global cognitive scores in most studies. These findings, however, do not contradict previous reports suggesting that increasing age has differential effects on different cognitive domains. They are also consistent with previous reports that the direct effects of age on cognitive function is substantially reduced when consideration is also given to modifying factors such as health, physiological performance or psychosocial parameters. It is noteworthy that the effect of age on emotional outcomes was much more inconsistent with some evidence that, when factors such as illness and physical disability are taken into consideration, the association with increasing age, at least for depressive symptoms, is actually reversed.

Putative Predictive Factors

There was considerable overlap in risk factors significantly associated with both cognitive and emotional outcomes, albeit sometimes with different emphases. Higher SES was protective for both outcomes. It was intriguing to note that cognitive performance was related to emotional outcomes, and mood was related to cognitive outcomes emphasizing the reciprocal nature of emotion and cognition. These findings suggest either that the relationship between emotion and cognition is bidirectional, or that they are affected by a common underlying neurobiological (in some cases degenerative) process. Yet the committee could not identify any study which investigated these outcomes in combination.

Some interesting findings in single studies worthy of further investigation include for example, results that suggest biological markers for inflammation and poor sleep appear to be risk factors for both emotional and cognitive outcomes. Exposure to lead is a risk factor for cognitive decline. The results for hormone replacement therapy are mixed for cognitive outcomes but a single study suggests it is protective for emotional outcomes.

Educational Experience

Higher education was almost uniformly reported to be protective for both cognitive and emotional outcomes. One explanation of this may be the concept of cognitive reserve, as proposed by Stern, that higher education increases cognitive reserve (Scarmeas and Stern, 2004). A parallel explanation for its effects on emotional outcomes is suggested by the association of general intelligence with positive affect that, in turn, may act as an emotional reservoir in times of stress. However, it has been proposed that educational attainment is only a marker for other factors such as socioeconomic and environmental influences in childhood (Hall et al. 2000). An elegant attempt to "deconstruct" levels of education as a risk factor for cognitive performance, particularly as it pertains to African Americans, has been undertaken by Manly (Manley and Jacobs, 2001). She discusses the problems surrounding equating years of education with quality of education and the difference cultural attitudes towards testing may make on performance. Consideration of these issues may minimize the apparent poorer cognitive performance of African Americans, even after adjusting for years of education. It has been suggested that literacy may be a better measure of functional education than years of education (Mehta et al. 2004).

Other Major Risk Factors

Five groups of factors appear to be of major significance in determining cognitive and emotional outcomes and deserve further exploration. They are cardiovascular risk factors, psychosocial risk factors including mood, genetic factors, physical activity, and the effects of chronic illness..

Cardiovascular risk factors

The committee's review highlights the increasing number of published studies suggesting that traditional risk factors for cardiovascular disease are also risk factors for cognitive decline. Cardiovascular (CV) risk factors encompass a rather broad field including factors which increase the risk for CV disease as well as actual diseases such as diabetes and hypertension.

CV risk factors can be classified into 'non-modifiable', lifestyle, and physiologic or mediating factors leading to cardiovascular disease. The role of 'non-modifiable' factors, such as age, education, and genetic susceptibility is discussed elsewhere in this document. Modifiable lifestyle factors include an individual's choices about diet, smoking, physical activity, alcohol intake and sleeping habits. Many of the modifiable risk factors are hypothesized to mediate vascular and neuronal damage via more physiologic CV risk factors (such as levels of blood pressure, lipids, homocysteine, glucose homeostasis, inflammation, body weight [or body mass index (BMI)], and hormones [e.g., estrogen]). Of this list, hypertension, BMI, heart disease, diabetes and smoking were the most frequently cited in this review, either as a primary predictor or confounding variable in the main analysis.

There are now several studies suggesting that hypertension increases the risk for cognitive decline. Hypertension increases the risk for vascular and endothelial damage in addition to small and large artery disease, and disrupts the blood brain barrier (Baumbach

1994; Faraci and Heistad 1990; Nag 1984). There is also evidence that blood pressure related changes may act directly on neurons through mechanisms such as inflammation and oxidative stress. Based on our review, this finding is the most robust across studies. Out of nine studies reporting collection of data on hypertension, even though definitions and methods of ascertainment may have differed across studies, five showed a significantly increased risk for cognitive decline. There were no reports suggesting hypertension protected against cognitive decline. In three studies, the use of anti-hypertensive medications was used as a control variable, not as a primary independent factor. In addition to the studies reviewed here, blood pressure has been associated with various measures of brain health, including magnetic resonance images of white matter lesions (Dufouil et al. 2001; van Dijk et al. 2004), hippocampal atrophy (Korf et al. 2004), clinical dementia (Launer et al. 2000), and neuropathologic markers of AD (Petrovitch et al. 2000) . There is some evidence from observational studies that treating elevated levels of blood pressure may reduce the risk for cognitive impairment.[67] Randomized trial results were mixed. Two trials were positive: dementia as outcome (Forette et al. 2002); dementia or cognitive decline associated with recurrent stroke as outcome (Tzourio et al. 2003)). One trial in which cognitive decline was the outcome was negative (Lithell et al. 2004).

Interestingly, seven studies reported on the association of BMI with cognitive outcomes. The three that did report on the significance of BMI suggest it may be a risk factor for cognitive decline. BMI may represent an indirect measure of peripheral metabolic, hormonal, or inflammatory responses that, in some way, modify central nervous system activity. Eleven studies have reported on smoking, however, eight included smoking only as a confounding variable for the main analysis. Diabetes also emerges as a risk factor for cognitive decline, whereby three studies report a significantly increased risk for cognitive decline and one showed no association.

Findings on other CV risk factors are not consistent and need to be replicated, for example, studies of sex steroid hormones report risk is increased, decreased, or not related to cognitive decline. Other factors, including alcohol intake, homocysteine, inflammation, and diet, have only been examined in one study. It should be noted that some of these CV factors have been examined in association with AD. In those studies, for instance, diabetes emerges as relatively robust risk factor (Ott et al. 1999; Luchsinger et al. 2001).

Despite the increase in interest in this area, the committee's review makes clear that there are still relatively few studies that examine CV factors as the *primary* risk factor of interest. The role of new cardiovascular risk factors, such as inflammatory markers, should also be investigated.

The 'lessons' to learn from the CV studies are: 1) prospective follow-up data are important to obtaining risk factor – outcome associations that are relatively free of reverse causality; 2) multiple outcome measures of brain aging and health are needed to support an anatomical and functional basis of effect; and 3) add-ons to existing studies,

either in the form of additional analyses or new data collection, will provide unique means to study new risk factors.

Guidelines for assessing observational evidence from epidemiologic studies could be recommended for future studies. In general, risk factors that are identified for interventions should be established with a similar critical level of evidence that we now have for blood pressure. Given such evidence, decisions could be made to move forward on randomized clinical trials specifically designed to change rates of brain aging. Cognitive outcomes could, in a very cost-effective way, be added to on-going trials designed to reduce cardiovascular risk factors and disease. The ACCORD-MIND sub-study is a good example of such leveraging. The National Heart, Lung and Blood Institute has mounted a very large trial designed to reduce CV risk in diabetics, and in a subset, an NIA-funded ancillary study was designed to test whether the interventions also reduce the risk for cognitive impairment and pathologic changes in brain structure.

Evidence of cerebral pathology in the committee's review was also associated with poorer cognitive and emotional outcomes. Two potentially protective factors emerged; the use of NSAIDs and aspirin presumably may modify, via neural protection, the risk conferred by cerebrovascular disease. The association between cerebrovascular disease, especially as indicated by stroke and both cognitive and emotional health, has long been established. Microvascular pathology (in the absence of frank stroke) also seems to negatively impact cognition (e.g. Kovari et al. 2004), though the area is greatly understudied. Aside from the studies in our survey, the literature focusing on cerebrovascular disease (in the absence of frank stroke) and emotional health is scant at best. Small, focused studies generally have found an association between cerebrovascular disease and late-life depression (especially late-onset depression, e.g., Camus et al. 2004; Steffens and Krishnan 1998; Thomas et al. 2004 for reviews), but very little is known about the relationship between cerebrovascular disease and emotional health more generally. The relation between cerebrovascular pathology and both cognitive and emotional health in late-life is of particular relevance, given that many risk factors for cerebrovascular disease are modifiable.

Depression and Anxiety

The committee's review suggests that a history of low mood (i.e. symptoms of depression or anxiety) is associated with both poorer cognitive and emotional health in late-life. While it has long been recognized that mood disorders frequently recur (and four out of five studies that we reviewed found that low mood at an earlier time point was associated with low mood at a later time point), the potential relationship between low mood and future cognitive decline has only recently been raised and thus far has not been well-studied, despite representing a potentially substantial public health concern. Two articles that the committee reviewed reported that low mood predicts subsequent cognitive decline. [18, 29] This finding is similar to those reported from smaller studies published in recent years (Alexopoulos et al. 1993; Bhalla et al. under review; Comijs et al. 2004; Paterniti et al. 2002; Wilson et al. 2004; Yaffe et al. 1999; see Jorm 2000 for a review of earlier published work). The committee's review focused on risk factors for cognitive decline in late-life and not dementia *per se*. Nevertheless, there is a growing body of

literature suggesting that a lifetime history of mood disorder increases one's risk of developing cognitive decline *and* future dementia. There are substantial limitations to our understanding of the cognitive course of depression; surprisingly little is known about the type or types of dementia for which individuals with a history of minor or major depression are at risk. There is substantial evidence that late-life depression is associated with cerebrovascular changes and other structural abnormalities. Individuals with late-life depression also seem to be at risk for developing AD. The various research findings among those with late-life depression have thus far been difficult to reconcile. As novel cognitive enhancing and dementia therapies are developed, it is likely that they will be most efficacious during the earliest and even pre-clinical stages. The challenge is to identify (1) the phenotypes and trajectories and (2) associated markers. Future studies should be prospective and employ more detailed and sensitive cognitive measures than the gross screening measures that have frequently been used in the past (e.g., the MMSE) in combination with well-defined and carefully derived cognitive disorder diagnoses.

Psychosocial Factors

Our literature survey also suggests that there is a substantial association between psychosocial factors (especially emotional support/social networks, SES and stress) and both cognitive and emotional health in late-life. One recent study found that the stress of caregiving was a risk factor for cognitive decline.[57] Most of the remaining studies that focused on psychosocial factors and cognitive change identified protective factors. For example, three studies found that higher SES protects cognitive functioning over time.[16, 56, 86] Two studies found that cultural factors protect against cognitive decline.[16, 37] Two studies found that social engagement and/or support protects against future cognitive decline.[7, 77] One study found that instrumental self-efficacy or believing that one can handle the instrumental aspects of life was a protective factor for memory.[76]

Physical Activity

There is growing evidence that physical activity may protect against cognitive decline and dementia in older adults. Three longitudinal, observational studies that met our inclusion criteria have investigated whether physical activity is associated with cognitive decline, and all three found that elders who exercise are less likely to experience cognitive decline. One study followed mostly elderly white, community-dwelling women without baseline cognitive impairment or physical limitations. [92] Women with greater physical activity at baseline (measured by blocks walked or by total kilocalories expended) were less likely to experience cognitive decline over the 8 years of follow-up after adjusting for age, education, comorbid conditions, smoking, estrogen, and functional limitations. Another study found an association with energy expended from strenuous, but not moderate, activities and preservation of cognitive function over 2-3 years in 1,011 community-dwelling elders[4]. The subjects in that study were part of a well-functioning group of elders and the measurement of physical activity included daily activities around the house. In the third study, a cohort of 3,734 Japanese-American men, a physical activity index was negatively correlated with score on a global measure of cognitive function, even after adjustment for possible confounders.[16]

Several interrelated mechanisms have been proposed to explain the association between physical activity and cognitive decline, including vascular disease, inflammation, and neurogenesis. There is consensus that low physical activity increases the risk of certain vascular diseases and vascular risk factors, including coronary heart disease, hypertension and diabetes. There also is a growing body of evidence that vascular disease, in turn, increases the risk and severity of cognitive decline and AD. Therefore, low physical activity could increase the risk of cognitive decline and dementia by increasing ischemia and atherosclerosis associated with vascular disease. There also is evidence that low physical activity is associated with higher levels of inflammatory markers in the blood (e.g., C-reactive protein). Inflammation, in turn, has been associated with an increased risk of cognitive decline and AD and also appears to increase the risk of cardiovascular disease. Therefore, it is also possible that low physical activity results in greater inflammation, which then increases the risk of cognitive decline and dementia either directly or through a vascular mechanism. Finally, physical activity appears to stimulate neurogenesis in mice. If these findings are confirmed in humans, neurogenesis could provide another pathway by which physical activity could protect against cognitive decline and dementia.

If physical activity were to protect against cognitive deterioration in the elderly, it would be of great public health importance because physical activity is relatively inexpensive, has few negative consequences and is accessible to most elders. Even if the effect size were relatively small, physical activity could have a dramatic impact on quality of life and health care expenditures at a societal level due to the large number of elders that could potentially benefit. There would be great benefit in conducting a large clinical trial to determine if physical activity, possibly in combination with intellectual activity, can prevent cognitive decline. Such a trial should also include emotional outcomes as there is increasing evidence that physical activity may improve mood and reduce anxiety.

Chronic Illness

The results from this survey strongly support prior reports describing an association between chronic illness and depressive symptoms in the elderly (Palinkas et al. 1990). Five of the studies in our survey reported that the presence of multiple chronic illnesses increased risk for poor emotional outcomes as did the presence of specific illnesses arthritis, cancer, lung disease, heart disease, and diabetes. [10,15,30,46,74] This latter finding supports the hypothesis that there may be specific disease constellations particularly associated with depression in the elderly (Penninx et al. 1996).

The studies utilized different outcomes (depression, anxiety, and negative affect) and measured chronic illness and its effects in a variety of ways from simple responses to enquiries about health status[15] to a more formal structured review of illnesses.[10] These differences explain most of the apparent discrepancies in our results. The two reports listed as finding no association between illnesses and emotional outcomes studied negative affect and anxiety symptoms.[47,62] The study on anxiety symptoms, while reporting no association between comorbid conditions in general and anxiety symptoms, did report that specific syndromes and conditions, such as hypertension and urinary incontinence, increase risk for incident anxiety.

It has been suggested that the prime mediator for the association between depression and chronic illness is the presence of functional disability (Black et al. 1998). However, in the study by Bisschop et al., it was reported that only in the case of stroke could the association between depressive symptoms and illness be accounted for by physical limitations.[10] This was not the case for cardiac disease, arthritis, cancer and lung disease, thus leaving the issue of causality uncertain. In the report by Hybels et al., depression was not associated with the presence of chronic disease as such, but rather, with scores of self related health suggesting that subjective aspects of illness were more strongly associated with depression than disease categories.[46]

Indeed, what is not always clear from these studies is the determination of causality between illness and depression. There is also, for example, increasing evidence that depression can make people vulnerable to illness through mechanisms such as oxidative stress, alterations of immune response, or increased platelet aggregation (Camus et al. 2004).

Most of the studies are cross-sectional in design making the assumption about the direction of the causal association uncertain. Large cohort studies that are longitudinal in design and follow the elderly before, during, and after the illness process would assist greatly in clarifying this issue. If these studies also included a cognitive component, they could provide an ideal design to explore the relationships between cognitive performance and emotional status during an illness process.

Genetic Influences

Genetic influences on cognitive and emotional health with aging are poorly understood at present. Only one gene, ApoE, has shown linkages to changes in cognition with aging. ApoE is a gene involved in the trafficking of cholesterol, and it has been known for some time to be associated with accelerated atherosclerosis. With the discovery of the link between one allelic variant of ApoE, designated the ε4 allele and AD (Saunders 1996), its associations with cognitive changes with aging have come under greater scrutiny in longitudinal studies. Before considering the observations from the literature search, some of the challenges in interpreting ApoE effects on cognition must be mentioned. First, at least for its impact on the incidence of AD, the presence of the ApoE ε4 allele exerts its effect in an age-dependent manner (Farrer 1997). Thus, ApoE effects on dementia incidence probably become minimal after age 80 or 85 years. The impact of ApoE in the elderly is further complicated by the fact that its allelic variations confer differential survival (Lee 2001; Fillenbaum 2002). Third, to the extent that ApoE is linked to a predilection for AD and possibly vascular disease (Eichner 2002; Wilson 1994), questions can be raised as to whether its impact on cognition is simply mediated by Alzheimer pathology and cerebrovascular disease. At present, there is inadequate data to address these concerns, but if the ApoE genotype did have an impact on cognition that preceded the onset of AD or vascular dementia by a decade or more, its importance on cognitive health would still be relevant.

The committee's review of the literature included 11 separate longitudinal studies. Although some studies found no impact of ApoE genotype on longitudinal measures of cognition [78, 88, 96], most have found selective or generalized effects [14, 22, 27, 37, 89, 92]. The fact that most of the studies revealed effects of ApoE genotype on cognition, independent of dementia, is impressive given the advanced age of the cohorts, which almost invariably were older than age 65 years. Different studies have made different claims about which cognitive domain was most prominently affected (memory[5]; naming and spatial abilities initially, global function later[14]). Only one study considered interactions with other risk factors, and that study, in fact, found that the ApoE genotype and cardiovascular disease showed a positive interaction.[45] Unfortunately, only a very small number of studies were encountered in this evaluation that addressed the issue of ApoE effects on emotional health. No association between depression and the ApoE genotype was seen [12] or on measures of quality of life [13]. All of the cited publications except Graves[37], who studied Japanese-Americans, and Fillenbaum[27], who studied African Americans, involved people of European descent. More information is needed on people of other racial backgrounds.

Although genetic factors cannot be modified, knowledge of genetic risk factors for premature cognitive dysfunction could help to identify those at higher risk. At the present time, there is a consensus that there is no justification for determining ApoE genotypes in cognitively intact individuals because of the low predictive accuracy of this genotype for either subsequent cognitive impairment or dementia (National Institute on Aging/Alzheimer's Association Working Group 1996). Perhaps if there were other genes identified that also exerted effects on risk assessment and, if there were useful preventive therapies, genetic screening for late life cognitive impairment potential could be considered.

This literature review has demonstrated some intriguing links between the ApoE genotype and cognition, but more work needs to be done to refine the relationship further. As additional genes linked to cognitive impairment and dementia are found, large population databases will be critical to investigating associations with those new genes (which are likely to be weaker than ApoE), and to investigating interactions between newly discovered genes, ApoE, and other risk factors. On the other hand, research on the associations between genes and emotional health is still largely in its infancy. However, reports from the Swedish Adoption/Twin Study of Aging suggest that genetic influences play at least a modest role in psychological well being, personality development, and depressive symptoms in the elderly (Bergeman et al. 1991; Jansson et al. 2004). The cliché "more work needs to be done" is a gross understatement.

Additional Comments

There are a number of methodological issues that should be highlighted in relation to this report. The first is that these results are not based on a meta-analysis or quantitative summary as mentioned earlier. Rather, the goal was to identify those findings that were consistent across many studies. It is helpful that the major findings reported here emerge from studies conducted in many parts of the world, lending support to the fact the results are likely to be generalizable. As noted earlier, the studies included here had to have

large sample sizes and therefore the power to detect meaningful relationships; negative findings from small studies are hard to interpret. This report is therefore primarily focused on very strong findings, repeatedly observed in multiple studies in a variety of communities and populations. There would be great value now in conducting a systematic meta-analysis of each of the risks factors identified in this survey.

Second, the outcome of interest is not the presence or absence of a disease, but rather a continuous variable related to either cognition or emotion. As such, the strength of the relationships reported here tend to be related to the adequacy of the measures employed. Some studies had a wealth of measures of cognition or emotion. For example, some studies assessed cognition with a variety of tests across multiple domains (e.g., memory, language, and conceptualization) and then used a composite score as the outcome. These studies tended to have considerable power to detect an effect because they were not dependent on a single variable to capture the outcome of interest. Likewise, some studies that examined emotional health had several measures related to it, and could assess risk factors in relation to each of them, increasing the likelihood that a meaningful relationship would be found. However, this was uncommon. Most studies had a small number of measures that evaluated a limited number of aspects of either cognition or emotion. Thus, it is likely that only the primary variables predictive of cognitive or emotional health are emphasized in this report, as those relationships with weaker effects could easily have been missed, given the constraints of the studies conducted to date.

Third, this report identifies a number of individual lifestyle and health behaviors that alter risk for maintenance of cognitive and emotional health. The evidence suggests that combinations of these factors are more likely to be predictive of high function over time than any one factor alone. However, it is not yet possible to develop prescriptions on an individual basis. Moreover, individuals who have optimal patterns of behavior may still demonstrate declines in function. That is to say, that the factors reported here should not be considered deterministic in any fashion. The limitations of this review, as outlined above, suggest that a number of important factors remain to be identified, which may play an important role in altering outcomes.

Finally, it is important to note that much work remains to be done in order to capture some important aspects of function satisfactorily. The best example of this is the assessment of functional status in daily life, where most existing measures, particularly those used in epidemiological settings, have substantial ceiling effects. In the suggestions at the end of this report, the committee details the specific areas where improved measurement capacity would be particularly beneficial for future studies.

Conclusions

There is now widespread public interest in developing strategies to maintain or enhance cognitive and emotional health in the elderly as witnessed by the recent campaigns of the American Association of Retired Persons and the Alzheimer's Association. From this survey, the committee concludes that cognitive decline and emotional distress in the elderly involves multiple pathophysiological and psychosocial processes that might be masked if the study outcome is a single disease. Thus, research that focuses on

preserving cognition and emotion may well identify a different set or combination of risk factors and thus different prevention strategies for healthy elderly subjects than would research on single disease outcomes. Moreover, as is stressed in the report, future research in the field of cognitive and emotional health must study both simultaneously, as cognition and emotion in aging are inextricably linked. One of the conclusions of this survey may be that our current scientific paradigm of exposure-outcome is too limited and does not handle well the interrelatedness of the multiple exposures where in certain circumstances outcomes can also be exposures.

The research community should therefore pursue the avenue of brain health maintenance with as much vigor as is brought to the quest to understand the pathophysiology of brain disease. The committee wishes to emphasize, however, that the goals of health promotion and disease prevention are complimentary and not conflicting. As this survey demonstrates, research into the factors involved with healthy brain aging has lagged well behind research into understanding brain disease. For example, information with regard to healthy brain aging had to be extrapolated from studies that had a predominantly disease oriented focus. With the current demographic trends increasing exponentially the number and percentage of the old, and in particular the oldest old in our population, we hope that this report stimulates a discussion among the leading scientists involved in aging research, including the Institutes directly involved with this project, to map a future research agenda which includes consideration of brain health maintenance as well as disease prevention.

The committee therefore suggests the following:

1] Secondary analyses

The committee is impressed with the large amount of information on cognitive and emotional outcomes which is potentially available in the currently funded large cohort studies both from the studies included in this review and the much larger number of studies included in the CEHP database (http://trans.nih.gov/CEHP), maintained at NIH. Only a limited amount of information has so far been published. A major effort should be made to encourage secondary analyses of data from these studies which could attain greater degrees of outcome specificity for cognitive and emotional health. This would require consideration of several issues:

a) Funding mechanisms including federal and non federal sources

b) Access to data - The NIH has established a data sharing agreement for NIH-supported studies. However, there needs to be sufficient documentation to make data interpretable and the data needs to be in manageable formats. Funding for this task should be considered when developing programs for secondary analyses. An appropriate consultation with the study primary investigators would be necessary.

c) Combined analyses (Creating consortia) - It is likely that for many risk factors a single study will have insufficient power to determine associations. It is also likely that cognitive and emotional health is a consequence, not of a single factor but the collective and interactive effects of many factors which will be difficult to demonstrate from the database of a single study. Therefore, the development of

consortia to analyze data from multiple studies should be encouraged. However, this approach is likely to have limitations based upon the compatibility of study design and information gathering between studies, and may be feasible only with a narrow focus and a concerted effort to harmonize the data from the studies (specified outcome with a limited number of factors).

d) In order to encourage secondary analysis, the NIH should consider establishing a support structure. It could be limited to a committee which would help promote the concept and develop Requests for Applications for specific projects. It could also be a more permanent structure the equivalent of Alzheimer's Disease Centers' National Alzheimer's Coordinating Center, that could advise potential researchers in developing their proposals in view of the compatibility issues described above, to assist in conducting harmonized analysis and to assist in the organization of a suitable consortium of studies.

e) This support structure (or a separate organization) could also act as a vehicle to support or conduct analyses similar to the Cochrane reviews http://www.cochrane.org/reviews/revstruc.htm, looking at the evidence systematically for particular risk factors on a rolling basis with quality assessment and integration as they are published. This by itself would be a valuable exercise in understanding the potential for prevention of the risk factors reviewed.

f) As the relationship between emotion and cognition appears to be complex and bidirectional and may be the result of a common underlying process, analyses of combined outcomes of cognitive and emotional health should be encouraged.

2] Development of standard questionnaires to measure cognitive and emotional health

While many studies contain information on cognitive and emotional health including such concepts as resilience, there is no agreement on the questionnaires used. Each study has its own unique battery of tests and questionnaires making comparisons between studies and combining data from studies difficult.

The committee proposes that an attempt be made to construct a questionnaire for cognitive and emotional health which could be used in current large cohort studies and be recommended for use in future studies. This proposed questionnaire needs to be multi-dimensional but as brief as possible making it useful for large cohort studies without increasing too much the burden for the participants of the study. Such questionnaires need to demonstrate longitudinal validity over a reasonable follow up period. The committee wishes to emphasize that this proposal is not intended to curb the creativity of research groups to develop unique methods of capturing and measuring these often complex concepts; it is meant to be complementary to these efforts. The standard questionnaire could be of particular use as an addition to studies that don't have cognition or emotion as their primary focus.

The development of the questionnaire could be accomplished in several ways:

a) The formation of an expert committee with the development of a questionnaire for use in epidemiological studies as its charge followed by publication and promotion of its findings and encouragement of its use.

b) The formation of a research team which would not only develop the questionnaire but try to test its reliability and validity. To accomplish this, the questionnaire would be administered to a select number of participants in current large cohort studies with the permission of the study investigators and then follow the participants over time. This process would allow for a more rigorous test of the proposed questionnaire making it more likely to be accepted by the scientific community. The model proposed here was the model used by The Consortium to Establish a Registry for Alzheimer's Diseases (CERAD), which was very influential in developing standardized methods to establish the clinical diagnosis of AD.

3] The use of biochemical markers

Modern laboratory technology now allows multiple analyses of potential biochemical markers from a single blood sample, thus making this approach feasible in large cohort studies. For example, measurements of lipids, insulin resistance, endothelial dysfunction, oxidative stress and inflammation can be accomplished from one sample. This approach has been enormously successful in identifying cardiovascular risk. As there appears to be a considerable overlap between the risk for cardiovascular disease and the risk for brain disease, the use of these markers should be supported in all large cohort studies with cognitive and emotional health as outcomes. Smaller more detailed studies may also be useful to test feasibility and to identify the most useful candidates amongst the large number of possible markers.

4] The use of brain imaging

Because of the cost involved and the relative novelty of the technology, there is little work on longitudinal aspects of brain imaging in aging, particularly in healthy populations. More work needs to be done because, however costly, the information is extremely valuable. Consortia of imaging sites could ease the burden. The recently launched NIA Alzheimer's Disease Neuroimaging Initiative is an attempt to discover the optimal imaging sequences and optimal strategies for standardizing imaging across multiple sites. As the technology continues to improve, the potential for neuroimaging to enhance our understanding of brain aging is unlimited.

5] Genetic research

As is the case with biological markers, advances in technology now allow for multiple genetic investigations from single blood samples. So far, this area has largely been focused on disease states with few exceptions, but genetic studies of successful aging should be encouraged (for example, investigations into the serotonin system as well as the apolipoprotein and related systems). Large cohort studies could provide DNA samples for the necessary extensive genetic testing and should be encouraged to do so.

6] Prevention Trials

Ultimately, investigations into factors associated with successful aging should lead to interventions. These interventions must be properly evaluated in properly designed studies. Prevention trials, however, present with enormous logistic and design issues which need very careful consideration before implementing in addition to deciding upon an appropriate intervention. The addition of cognitive and emotional outcomes to

ongoing trials designed for other primary outcomes, such as cardiovascular disease, may prove to be a very feasible and cost effective way to conduct these trials.

7] Changing the paradigm of successful cognitive and emotional aging

The conceptual basis of successful cognitive and emotional aging has only begun to be explored. This review has focused on medical, psychological and emotional factors that influence cognitive and emotional function as narrowly defined by the committee. However, this is just brushing the surface of a very complex problem. As our society transforms the model of aging from "survival" to "successful," there may be a revolution in ideas about what constitutes cognitive and emotional aging. Do resilience, mastery, self-efficacy and vitality cover the conceptual landscape? What should be the range for expectations about successful cognitive and emotional health in the elderly? Biomedical researchers should join forces with investigators from other disciplines such as social sciences, bioethics amongst others to create a new concept.

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Appendix

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