

Review Article

The NIH Cognitive and Emotional Health Project

Report of the Critical Evaluation Study Committee

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Abstract

Background: The Cognitive and Emotional Health Project (CEHP) seeks to identify the demographic, social, and biological determinants of cognitive and emotional health in the older adult. As part of the CEHP, a critical evaluation study committee was formed to assess the state of epidemiological research on demographic, social, and biological determinants of cognitive and emotional health.

Methods: Criteria for inclusion in the survey were large cohort studies, longitudinal in design, participants predominantly 65 years or older, with measurements of both cognition and emotion, and information on a wide variety of demographic, psychosocial, and biological factors. North American and European studies, which met these criteria, were selected for the review. Outcome measures included cognition, cognitive decline, and cognitive function. For emotion, symptoms included depression and anxiety, positive and negative affect, subjective well being, mastery, and resilience.

Results: Ninety-six papers were identified that addressed cognitive and emotional outcomes. A large variety of risk factors were consistently identified with cognitive outcomes, particularly those previously associated with increased risk of cardiovascular disease. There was considerable overlap between risk factors for cognitive and emotional outcomes.

Conclusion: This review identifies a large number of lifestyle and health behaviors that alter the risk for maintenance of cognitive and emotional health. Large longitudinal cohort studies are a unique source to explore factors associated with cognitive and emotional health. Secondary analyses of these studies should be encouraged as should the development of standardized questionnaires to measure cognitive and emotional health. Future research in this field should study cognitive and emotional health simultaneously.

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Keywords:

Cognition; Emotion; Cognitive decline; Depressive symptoms; Anxiety symptoms; Risk factors; Education; Cardiovascular; Psychosocial; Physical activity; Chronic illness; Genetic

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† This article was written by authors in their capacity as NIH employees, but the views expressed in the article do not necessarily represent those of the NIH.

Preamble

The last century has witnessed a truly remarkable demographic transition that has dramatically increased the numbers and percentages of adults living until over the age of 65 years both in United States and in the rest of the world. This process, which has been termed the *New Longevity* and which shows no signs of abating, creates major challenges for our society [1]. One of these challenges, and one that has not escaped the attention of major national organizations such as the Alzheimer's Association and the American Association of Retired People, is the need to preserve optimal levels of cognitive and emotional functioning in this aging population. Thus, identifying the demographic, biological, and psychosocial factors that can help people maintain or enhance their cognitive and emotional health as they grow older becomes a major public health goal for this country. This report describes the findings of the Critical Evaluation Study Committee formed as part of the trans-National Institutes of Health (NIH; the National Institute on Aging, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke) Project on Cognitive and Emotional Health. The charge of the committee was to conduct a critical analysis of the existing scientific literature pertaining to factors involved in the maintenance of cognitive and emotional health in the adult.

1. Introduction

There is as yet no universally accepted definition of what constitutes cognitive and emotional health in the older adult. The definition of cognitive health adopted by the Critical Evaluation Study Committee was that cognitive health as it pertains to the older adult 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 older adult 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 risk factors that preserve cognitive function or prevent cognitive decline. Although 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 also be identified as factors for cognitive decline. For example, there are other common age-related non-AD pathophysiologic processes that could produce cognitive decline or cognitive impairment either singly or collectively, including milder forms of cerebrovascular disease or cell loss owing 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 [2]. 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 [3]. Individuals with cognitive decline are at much greater risk for having 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 [4]. 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. These observational findings suggest implementation of alternative or complementary strategies for reducing risk for dementia.

Studies of healthy brain aging, such as the MacArthur Studies of Successful Aging [1], are much less common than studies of cognitive decline. Results from these studies suggest that "successful" aging should be distinguished from "normal" aging. They also tend to emphasize psychosocial factors as major influences in maintaining cognitive health and suggest appropriate prevention strategies involving lifestyle changes. One ongoing intervention trial, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE), found that some cognitive processes such as speed of processing and reasoning ability, can be enhanced at least temporarily in the older adult by intellectual exercises [5]. 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" [6]. 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. Current expectations for healthy cognitive aging may 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 prospect of older adults with a much broader range of physiologic and psychosocial functioning surviving into the eight decade and beyond, these expectations may well change.

Similarly, the committee 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 responses. 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 older adult 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 Study, 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 [7]. 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 [8]. 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 that suggest a more complex relationship between this trait and the sociodemographic context [9]. 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. For example, Carstensen and colleagues, 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, maintaining social networks, emotional regulation, and cognitive processing [10].

Emotional health and cognitive health are often considered separately in research studies, as are psychiatric disorders and dementing disorders. At least 2 recent NIH-sponsored reports 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 [11, 12]. Both reports suggested more comprehensive approaches to the disorders of the older adults involving collaborations across NIH Institutes. The committee also concluded that consideration of emotional health separate from cognitive health is impractical and uninformative because emotion is involved in cognitive processes and vice versa. Three biological processes have been identified to explain the interaction of cognition and emotion: gluco-corticoid secretion and brain-derived neurotrophic factor regulation of synaptic

activity (both stress related) [13], and cerebrovascular disease, which may be a risk factor for both cognitive impairment and depression [14].

There has been considerable interest recently in health promotion strategies in neuropsychiatric 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 is based not only on 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 solely on a disease of the elderly. Thus, 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 2 goals of disease prevention and health promotion are complementary [15]. It also is probable that the guidelines for healthy individuals to maintain health may be different than those recommendations for at-risk subjects to prevent disease.

The remainder of this report describes the formation of the committee as part of the Cognitive and Emotional Health Project and the findings and suggestions of this committee.

2. The Cognitive and Emotional Health Project

Three Institutes, the National Institute on Aging (NIA), the National Institute of Mental Health (NIMH) and the National Institute of Neurological Disorders and Stroke (NINDS) joined efforts to launch a new trans-NIH initiative, The Cognitive and Emotional Health Project. This project seeks to identify the demographic, social, and biological determinants of cognitive and emotional health in the older adult. Staff from the NIA (Dr. Molly Wagster), the NIMH (Dr. Bruce Cuthbert), and the NINDS (Dr. Emmeline Edwards) coordinates 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 trans-Institute task force, including a workshop held in July 2001 entitled, “Cognitive and Emotional Health: The Healthy Brain Workshop” (HBW). A description of these activities is included in the website <http://trans.nih.gov/CEHP/>.

One of the conclusions of the HBW was 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 should be formed to conduct a critical analysis of existing studies before making specific recommendations.

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 in the adult. Based on 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 offer suggestions for future research opportunities—for example, the promotion of and identification of opportunities for ancillary or secondary data analytic studies, the addition of 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.

3. The critical review

3.1. 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 on the presumption that some of these characteristics comprise strong protective factors against many of the disorders and illnesses associated with the elderly.

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.

3.2. Criteria for studies to include in the critical analysis

Because a major goal of the Cognitive and Emotional Health Project was to “assess the state of longitudinal and epidemiologic 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 also decided to concentrate on those studies either observational or interventional, that were large cohort, predominantly with participants 65 years or over, longitudinal in design, and incorporated 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 epidemiologic studies, a longitudinal design confers considerable advantage in determining causation as compared with a cross-sectional design involving a single outcome measurement. However, the committee did make 2 exceptions to the criteria for longitudinal design. Because of the concern that there may be few studies with emotional outcomes involving multiple measurements over time, the committee decided to also examine studies with emotional outcomes that used cross-sectional designs. An exception also was made for cognitive outcomes studies in which biological data were gathered some years previously in the setting of a longitudinal 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 epidemiologic and other large cohort studies supported by the NIH to determine whether it was feasible to operationalize these “ideal” criteria. Questionnaire responses from 80 studies have been recorded in a Web-based database maintained at the NIH (see <http://trans.nih.gov/CEHP/hbq/search.asp>). Many of these studies did include some measurements of the important domains of cognitive and emotional health that might yield useful information; however, they did not 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 greater than 500
- Age predominantly 65 and over
- Longitudinal in design

Table 1
Studies included in the critical evaluation

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

- At least one follow-up evaluation of cognitive function, or
- Single evaluation of cognitive function where exposure is measured years before 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) also was added, although the study was not included in the NIH database.

Members of the committee were aware of the fact that there were a number of large existing international studies

not supported by the 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 (PAQUID) Study, Swiss Interdisciplinary Longitudinal Study, Longitudinal Aging Study Amsterdam, Kungsholmen Project, and Amsterdam Study of the Elderly. Table 1 shows all of the 36 North American and European studies included in this report.

A bibliographic search for publications pertaining to the identified studies was conducted using PubMed supplemented by Ovid/PsycINFO; 1,880 articles were identified. Abstracts from these articles were sent to the committee members for preliminary review to determine whether they met criteria for inclusion in the analysis. From this preliminary review, 266 abstracts were selected for full text re-

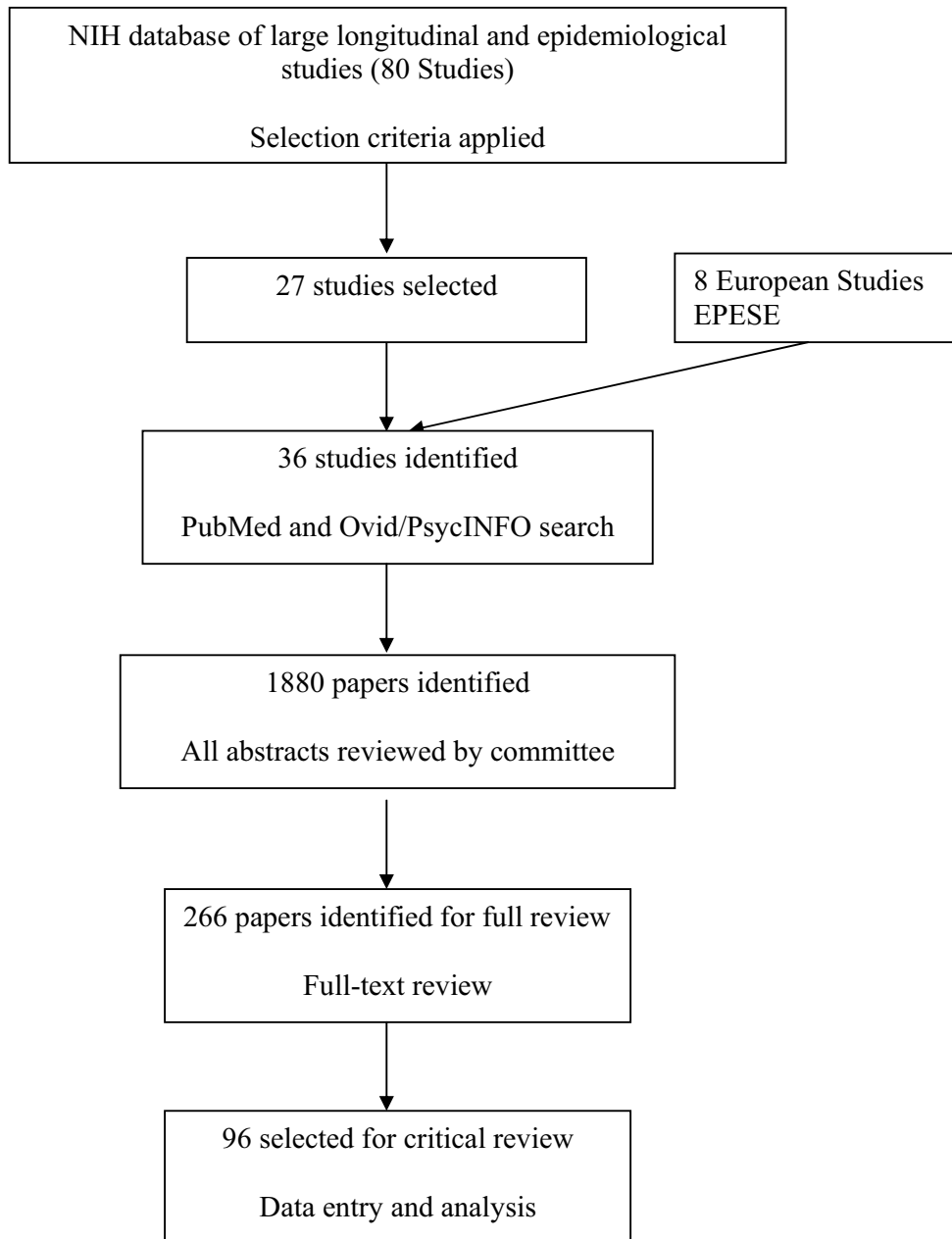


Fig. 1. Selection and review process.

view. The texts were reviewed by a doctoral candidate from Indiana University, Sven Klingemann, 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 reviewed independently 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 preselected risk factor categories, the forms contained a provision for

write-ins. The entered data are 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.

3.3. 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 3 levels. First, it was decided that each study should be represented by a single

Table 2
Variables examined as predictors of cognitive outcomes

Factor	Total Number of Publications*	Significant Risk†	Significant Protection†	No Significant Association†	Adjusted For‡	Survey Bibliography: Appendix Reference Numbers§
Age	20	6	0	1	13	A4,A16,A24,A27,A37,A38,A44,A48,A52,A57,A61,A64,A66,A70,A75,A85,A88,A94,A95,A96
Alcohol	9	0	2	0	7	A26,A27,A32,A58,A64,A70,A75,A91,A95
Alcoholism	1	1	0	0	0	A32
Antihypertensive medication	3	0	0	0	3	A23,A44,A67
Aspirin	3	0	1	1	1	A48,A50,A94
BMI	7	3	0	0	4	A3,A24,A27,A58,A59,A70,A95
Baseline cognitive function	3	0	2	0	1	A18,A37,A72
Being married	1	0	0	1	0	A77
Biological factors—inflammation	1	1	0	0	0	A95
Brain imaging—infarct/white matter lesions	2	2	0	0	0	A52,A85
Brain imaging—atrophy	1	1	0	0	0	A52
Chronic disease—arthritis	2	0	0	0	2	A27,A48
Chronic disease—cancer	1	1	0	0	0	A27
Chronic disease—osteoporosis	2	1	0	0	1	A27,A59
Diabetes	8	3	0	1	4	A24,A27,A39,A45,A48,A58,A70,A94
Diet	1	0	0	1	0	A64
Education	20	0	8	1	11	A4,A16,A24,A27,A34,A37,A38,A44,A52,A58,A61,A64,A66,A70,A73,A85,A88,A94,A95,A96
Female	13	1	0	4	8	A2,A5,A14,A33,A37,A38,A44,A45,A66,A72,A85,A88,A95
Functional/physical disability	4	1	0	1	2	A1,A27,A59,A76
Genetic factors	11	6	0	3	2	A5,A14,A22,A27,A29,A37,A78,A88,A89,A92,A96
Health	5	0	0	0	5	A7,A63,A75,A93,A95
Heart disease	10	1	0	3	6	A7,A26,A44,A45,A48,A57,A69,A70,A78,A93
Homocysteine	1	0	0	1	0	A49
Hormones	5	2	2	1	0	A27,A40,A61,A70,A71
Hyperlipidemia	4	1	0	1	2	A21,A24,A58,A94
Hypertension	9	5	0	0	4	A24,A36,A44,A45,A55,A57,A64,A70,A93
Interaction genetic	4	2	0	2	0	A21,A67,A78,A92
Lead exposure	1	1	0	0	0	A75
Lung	2	0	2	0	0	A4,A16
Memory complaints	1	1	0	0	0	A22
Menopause	3	0	1	0	2	A58,A63,A71
Mental health	1	0	0	0	1	A57
Mood (low)	5	2	0	0	3	A18,A27,A29,A77,A91
Multiple chronic diseases	4	0	0	0	4	A18,A27,A77,A95
NSAIDS (excludes aspirin)	4	0	1	2	1	A48,A50,A72,A95
Other	4	0	1	1	2	A27,A38,A43,A70
Physical activity	4	0	3	0	1	A4,A7,A16,A93
Poor sleep	1	1	0	0	0	A29
Psychosocial factors—Cultural	2	0	2	0	0	A16,A37
Psychosocial factors—emotional support/social networks	3	0	2	1	0	A1,A7,A77
Psychosocial factors—other	1	0	0	1	0	A1
Psychosocial factors—personality	2	0	1	0	1	A57,A76
Psychosocial factors—stress	1	1	0	0	0	A57
Psychotropics	2	0	0	0	2	A27,A57
Race	6	2	0	1	3	A4,A27,A52,A64,A70,A95
Residence	2	0	0	0	2	A3,A66
SES	8	0	3	1	4	A16,A24,A37,A56,A63,A70,A77,A86
Sensory handicap	3	0	0	1	2	A7,A33,A39
Smoking	11	2	0	1	8	A24,A27,A31,A38,A58,A59,A64,A66,A70,A75,A95
Stroke/TIA	7	3	0	1	3	A21,A44,A45,A59,A66,A69,A72
Thyroid	1	0	0	0	1	A27
Vitamins	3	0	2	0	1	A42,A60,A64

* The number of publications that included the factor in their analyses.

† A significant association and its direction.

‡ The factor was adjusted for in determining the final risk model but that the direction of the association was not provided.

§ References cited with the prefix letter A appear serially in the appendix.

Table 3
Variables examined as predictors of emotional outcomes

Factor	Total Number of Publications*	Significant Risk†	Significantly Protective†	No Significant Association†	Adjusted For‡	Survey Bibliography: Appendix Reference Numbers§
Age	8	2	2	1	3	A11,A30,A51,A53,A65,A68,A74,A83
Alcohol	2	0	0	1	1	A62,A79
BMI	2	0	0	0	2	A68,A83
Baseline cognitive function	3	0	2	0	1	A12,A65,A80
Being married	7	1	2	2	2	A9,A12,A30,A47,A62,A65,A74
Biological factors	2	1	0	1	0	A20,A79
Biological factors inflammation	3	2	0	1	0	A20,A68,A82
Chronic disease—gynecological	1	0	0	0	1	A87
Chronic disease—arthritis	2	1	0	1	0	A10,A65
Chronic disease—cancer	1	1	0	0	0	A10
Chronic disease—lung	1	1	0	0	0	A10
Chronic disease—other	2	1	0	0	1	A51,A74
Cognitive factors—cognitive change	1	0	0	0	1	A8
Cognitive factors—cognitive function	8	1	3	0	4	A9,A15,A30,A47,A65,A74,A83,A87
Diabetes	3	2	0	0	1	A51,A65,A83
Education	8	0	4	2	2	A12,A15,A30,A47,A51,A65,A74,A83
Family history	2	0	0	0	2	A8,A74
Family size	1	0	0	1	0	A15
Female	7	3	0	1	3	A6,A12,A30,A51,A68,A74,A83
Functional/physical disability	9	7	0	0	2	A6,A9,A30,A46,A62,A65,A74,A82,A87
Genetic factors	1	0	0	1	0	A12
Health	7	0	3	2	2	A19,A28,A30,A46,A65,A79,A87
Heart disease	3	3	0	0	0	A10,A65,A81
Homocysteine	1	0	0	1	0	A79
Hormones	1	0	1	0	0	A87
Hyperlipidemia	2	0	0	1	1	A12,A83
Hypertension	2	1	0	1	0	A62,A80
Mental health	1	1	0	0	0	A74
Mood (low)	5	4	0	0	1	A12,A15,A30,A65,A74
Multiple chronic diseases	7	5	0	2	0	A10,A15,A30,A46,A47,A62,A74
Poor sleep	1	1	0	0	0	A62
Psychosocial factors—childhood	1	0	0	0	1	A8
Psychosocial factors—cog factors interaction	1	1	0	0	0	A84
Psychosocial factors—emotional support/social networks	8	0	6	1	1	A30,A46,A47,A51,A62,A65,A74,A87
Psychosocial factors—other	3	2	0	1	0	A15,A30,A84
Psychosocial factors—personality	3	3	0	0	0	A9,A47,A62
Psychosocial factors—religion	1	0	0	1	0	A30
Psychosocial factors—stress	6	5	0	0	1	A19,A28,A30,A35,A62,A74
Psychotropics	4	1	0	0	3	A46,A68,A83,A87
Race	3	1	1	1	0	A12,A30,A62
Residence	4	0	1	1	2	A6,A15,A51,A68
SES	3	0	2	1	0	A11,A15,A65
Sensory handicap	3	2	0	1	0	A51,A62,A65
Smoking	3	0	0	0	3	A68,A83,A87
Stroke/TIA	2	0	0	1	1	A10,A82
Vitamins	1	0	0	1	0	A79

* The number of publications that included the factor in their analyses.

† Significant association and its direction.

‡ The factor was adjusted for in determining the final risk model but that the direction of the association was not provided.

§ References cited with the prefix letter A appear serially in the appendix.

article for each risk factor on the outcomes 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 results reflected the overall results of the studies and was not biased by multiple reporting from a single study on a given outcome and 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) In the cognitive table, the committee chose to report only the significant findings. For example, a factor might be reported as having no significant risk for language yet a significant risk for memory. Thus, the significant risk for memory would be included in the cognitive outcome table, but the nonsignificant 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 much 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.

For both tables, cross-sectional and longitudinal findings were combined. The table on emotional outcomes incorporates articles reporting on anxiety, depression, dysphoria, negative affect, and loneliness. The structure the committee chose to impose made it difficult to include in the emotional outcome table the few articles that reported on positive outcomes such as positive affect, subjective well-being, mastery, or self-efficacy. The results from these articles are described separately in the text.

3.4. Summary of results

The literature review for cognitive and emotional outcomes is presented in Tables 2 and 3. 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 report. The best interpretation of this column is that the researchers found a significant association between the adjusted factor and the outcome in previous analysis, or that they assumed an association based on prior reports. Thus, for example, adjusting for age in studies with cognitive outcomes is based on the voluminous literature indicating that increasing age is associated with cognitive decline. The last column includes the reference numbers for all papers included in the second column (see Appendix, 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 (BMI). Details on

variables adjusted for in each article are captured in the committee's database but not presented in the summary tables of this report.

For cognition, the factors most consistently associated with poor outcomes included increasing age, hypertension, diabetes, stroke or transient ischemic attacks (TIAs), presence of infarcts or white matter lesions from brain imaging, low mood, and higher BMI ratings. The protective factors most consistently reported included 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) $\epsilon 4$ 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 included biological markers of inflammation, exposure to lead, alcoholism, poor sleep, cancer, and osteoporosis (all increasing risk for poor outcomes) and the personality characteristic of mastery, which was protective.

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

Factors significantly associated with emotional outcomes in single studies included poor sleep, which increased risk, and hormone replacement therapy, which was protective. The possession of the APOE $\epsilon 4$ allele was not significantly associated with emotional outcomes in a single study.

There were 7 articles, which are represented in both the cognitive and the emotional outcomes tables (Tables 2 and 3), that described the results of interactions between risk factors. Four of these analyzed the interactions between APOE $\epsilon 4$ and other risk factors. They reported that estrogen therapy was associated with less cognitive decline among $\epsilon 4$ negative but not $\epsilon 4$ positive women; $\epsilon 4$ carriers with atherosclerosis were at greater risk for cognitive decline than carriers without $\epsilon 4$; midlife high systolic blood pressure had a stronger adverse effect on cognitive function in persons with $\epsilon 4$, but this effect appeared to be modified by antihypertensive medication. Stroke and APOE $\epsilon 4$ may impair cognition through nonsynergistic mechanisms. Two articles discussed interactions involving educational levels. They reported that depression increased the risk for cognitive decline only in individuals with higher levels of education, and formal education accounted for the apparent significant protective effect of current oral estrogen replacement ther-

apy 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 [A17,A51].* Major factors associated with poor outcome in these domains 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 [A13,A47,A53,A54]. 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 ϵ 4 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. The Survey Bibliography includes 3 papers [A25, A41, A90] that are not incorporated into the tables because the data from these studies appeared in later studies that are included.

4. 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 that contain much information on these outcomes (e.g., 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 show 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 that have not yet been published, which raises 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 the committee's criteria, we have identified 21 that reported on cognitive outcomes and 12 that reported on emotional outcomes. It is likely, in fact, that all 80 studies recorded in the NIH database contain very useful information to explore risk factors for cognitive and emotional health. There were fewer studies in this review that had *positive* cognitive and emotional outcomes as the major focus (for example, the MacArthur Studies on Successful Aging and the Berlin Aging Study), but it appears that most of these studies would have the capacity to conduct such analyses from their databases. The reason for the relatively fewer number of published reports on these outcomes from this group of very productive investigators likely is that the primary focus of most of these studies was disease-oriented (involving the dementias, AD, Major Depressive Disorder) so that analyses on nondisease outcomes was a lower priority. This disease-oriented focus is represented in the current priorities of the NIH.

The grouping process, conducted for reasons of conciseness both for outcomes and risk factors, also resulted in a loss of information and understates the complexities of some of the relationships. It should also be noted that the individual risk factors reviewed were not necessarily defined by the same criteria, and their reported associations with cognitive or emotional outcomes all may not have been 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 also are consistent with previous reports that the direct effects of age on cognitive function is substantially reduced when consideration is given to modifying factors such as health, physiologic 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.

4.1. Putative predictive factors

There is 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 is 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. It suggests 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.

* References cited with the prefix letter A appear serially in the appendix.

Yet we could not identify any study that investigated these outcomes in combination.

Some interesting findings in single studies worthy of further investigation include, for example, that 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 therapy are mixed for cognitive outcomes, but a single study suggests it is protective for emotional outcomes.

4.2. Educational experience

Higher levels of education were almost uniformly reported to be protective for both cognitive and emotional outcomes. One explanation for this finding, proposed by Stern and others [4], is that factors such as educational achievement are capable of contributing to or maintaining a cognitive reserve. A parallel explanation for education's 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 higher education is only a marker for other risk factors such as deleterious socioeconomic and environmental influences in childhood [16]. 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 [17]. She discusses the problems surrounding equating years of education with quality of education and the different cultural attitudes toward testing may make on performance. Consideration of these issues may minimize the apparent poorer cognitive performance of older African Americans compared with older whites, 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 [18].

4.3. Other major risk factors

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

4.4. Cardiovascular risk factors

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

CV risk factors can be classified into “nonmodifiable,” lifestyle, and physiologic or mediating factors leading to CV disease. The role of “nonmodifiable” factors, such as

age, education, and genetic susceptibility is discussed elsewhere in this report. Modifiable lifestyle factors include individual 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 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.

Findings from several studies suggest that hypertension increases the risk for cognitive decline. Hypertension increases risk for vascular and endothelial damage in addition to small and large artery disease and disrupts the blood–brain barrier [19–21]. Additionally, there is evidence that blood pressure–related changes may act directly on neurons through mechanisms such as inflammation and oxidative stress. Based on our review of CV risk factors, the link between hypertension and cognitive decline was the most robust across studies. Out of 9 studies reporting collection of data on hypertension, even though definitions and methods of ascertainment may have differed across studies, 5 showed a significantly increased risk for cognitive decline. There were no reports suggesting hypertension protected against cognitive decline. In 3 studies, the use of antihypertensive medications was used as a control variable, not as a primary independent factor. In addition to the publications reviewed here, blood pressure has been associated with various measures of brain health, including evidence of white matter lesions [22,23] and hippocampal atrophy [24] using magnetic resonance imaging, clinical dementia [25], and neuropathologic markers of AD [26]. There is some evidence from observational studies that treating elevated levels of blood pressure may reduce the risk for cognitive impairment [A67]. Randomized trial results are mixed. Two trials were positive—one with dementia as the outcome [27] and one with dementia or cognitive decline associated with recurrent stroke as outcomes [28]. One trial looking at cognitive decline as an outcome was negative [29].

Interestingly, the association of BMI with cognitive outcomes was reported in 7 articles. The 3 that reported on the significance of BMI suggested high BMI 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 reports included data on smoking; however, 8 included smoking only as a confounding variable for the main analysis. Diabetes also emerged as a risk factor for cognitive decline, whereby 3 articles reported a significantly increased risk for cognitive decline, and 1 showed no association.

Findings on other CV risk factors are not consistent and need to be replicated. For example, studies of sex steroid

hormone therapy have reported risk for cognitive decline as increased, decreased, or not related. Other factors, including alcohol intake, homocysteine levels, inflammation, and diet, were examined in only one of the studies reviewed. 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 [30,31].

Despite the increase in interest in this area, our 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 for 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 anatomic 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 ongoing trials designed to reduce CV risk factors and disease. The Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) substudy 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 our review also was 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 affect cognition [32], although 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., [33–35]), but very little is known about the relationship between cerebrovascular disease and emotional health more generally. The relationship 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.

4.5. *Depression and anxiety*

Our 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. Whereas it has long been recognized that mood disorders frequently recur (and 4 of 5 articles 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 we reviewed reported that low mood predicts subsequent cognitive decline [A18,A29]. This finding from our review is similar to those reported from smaller studies published in recent years [36–41]. Our 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 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 preclinical stages. The challenge is to identify (1) the phenotypes and trajectories and (2) associated markers. Future studies should be prospective and use more detailed and sensitive cognitive measures than the gross screening measures that have been used frequently in the past (e.g., the MMSE) in combination with well-defined and carefully derived cognitive disorder diagnoses.

4.6. *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 [A57]. Most of the remaining studies that

focused on psychosocial factors and cognitive change identified protective factors. For example, 3 studies found that higher SES protects cognitive functioning over time [A16,A56,A86]. Two studies found that cultural factors protect against cognitive decline [A16,A37]. Two studies found that social engagement and/or support protects against future cognitive decline [A7,A77]. One study found that instrumental self-efficacy or believing that one can handle the instrumental aspects of life was a protective factor for memory [A76].

4.7. 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 3 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 [A92]. 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 to 3 years in 1,011 community-dwelling elders [A4]. 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 correlated negatively with score on a global measure of cognitive function, even after adjustment for possible confounders [A16].

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 owing 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 because there is increasing evidence that physical activity may improve mood and reduce anxiety.

4.8. Chronic illness

The results from this survey strongly support prior reports describing an association between chronic illness and depressive symptoms in the elderly [42]. 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 [A10,A15,A30,A46,A74]. This latter finding supports the hypothesis that there may be specific disease constellations particularly associated with depression in the elderly [43].

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 [A15] to a more formal structured review of illnesses [A10]. These differences explain most of the apparent discrepancies in our results. The 2 reports listed as finding no association between illnesses and emotional outcomes studied negative affect and anxiety symptoms [A47,A62]. 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, did 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 [44]. 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 [A10]. This was not the case for cardiac disease, arthritis, cancer, and lung disease, thus leaving the issue of causality uncer-

tain. 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 [A46].

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 [33].

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 would 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.

4.9. Genetic influences

Genetic influences on cognitive and emotional health with aging are poorly understood at present. Only 1 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 $\epsilon 4$ allele, and AD [45], its associations with cognitive changes with aging have come under greater scrutiny in longitudinal studies. Before considering the observations from our 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* $\epsilon 4$ allele exerts its effect in an age-dependent manner [46]. 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 [47,48]. Third, to the extent that *APOE* is linked to a predilection for AD and possibly vascular disease [49,50], questions can be raised as to whether its impact on cognition is simply mediated by Alzheimer pathology and cerebrovascular disease. Currently, there are 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.

Our review of the literature included 11 separate longitudinal studies. Although some studies found no impact of *APOE* genotype on longitudinal measures of cognition [A78,A88,A96], most have found selective or generalized effects [A14,A22,A27,A37,A89,A92]. 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 [A5]; naming and spatial abilities initially, global function later [A14]). Only 1 study considered interactions with other risk factors, and that study, in fact, found that the *APOE* genotype and cardiovascular disease showed a positive interaction [A45]. Unfortunately, we encountered only a very small number of studies that addressed the issue of *APOE* effects on emotional health. No association between depression and the *APOE* genotype was seen [A12] or on measures of quality of life [A13]. All of the cited studies except Graves [A37], who studied Japanese Americans, and Fillenbaum [A27], 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 identify those at higher risk. Currently, 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 [51]. 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.

Our literature review has found 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 (SATSA) suggest that genetic influences play at least a modest role in psychological well being, personality development, and depressive symptoms in the elderly [52,53]. The cliché “more work needs to be done” is a gross understatement.

4.10. Additional comments

There are a number of methodologic 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 different communities and populations. There would be great value now in conducting a systematic meta-analysis of each of the risks factors identified in our 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 used. 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 show 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 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 epidemiologic settings, have substantial ceiling effects. In the recommendations at the end of this report, we detail the specific areas in which improved measurement capacity would be particularly beneficial for future studies.

5. 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 pathophysiologic 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 in which, 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 our 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. Given that the number and percentage of the old, and in particular the oldest old, are increasingly exponentially 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 that 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 NIH database (<http://trans.nih.gov/CEHP>). 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 that 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 nonfederal 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 need 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 also 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 that 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 on the compatibility of study design and information gathering between studies and may be feasible only with a narrow focus and with a concerted effort to harmonize the data from the studies (specified outcome with a limited number of factors).
 - d) To encourage secondary analysis, the NIH should consider establishing a support structure. It could be limited to a committee that would help promote the concept and develop Requests for Application for specific projects. It could also be a more permanent structure similar to the Alzheimer's Disease Centers' National Alzheimer's Coordinating Center, that could advise potential researchers in development of their proposals in view of the compatibility issues described above, that could assist in conducting harmonized analysis and that could 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 for the factors reviewed.
 - f) Because 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 assessment of cognitive and emotional health that 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 show 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 do not have cognition or emotion as their primary foci.

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 epidemiologic studies as its charge, followed by publication and promotion of its findings and encouragement of its use.
 - b) The formation of a research team that would not only develop the questionnaire but 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 is the model used by CERAD (The Consortium to Establish a Registry for Alzheimer's Diseases), 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. Because 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 also may be useful to test feasibility and to identify the most useful candidates among 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 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 enormous logistic and design issues that need very careful consideration before implementing in addition to deciding on an appropriate intervention. The addition of cognitive and emotional outcomes to ongoing trials designed for other primary outcomes, such as CV 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. Our review has focused on medical, psychological, and emotional factors that influence cognitive and emotional function as we have narrowly defined it. 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 and bioethics, among others, to create a new concept.

Acknowledgments

The committee would like to acknowledge and thank the following for their contributions to the report: Sven Klingemann, Indiana University; Kathleen A. Lane, Indiana University; Tammy K. Rowe, National Institute on Aging; Laurel M. Gilligan, National Institute of Mental Health; and Stacey D. Chambers, National Institute of Neurological Disorders and Stroke.

External Reviewers: Carol E. Brayne, University of Cambridge and Dan G. Blazer, Duke University.

Alzheimer's & Dementia will publish all invited commentaries in the current as well as subsequent issues of this journal, thus creating a forum for ongoing dialogue among the proponents of different perspectives on this topic.

References

- [1] Rowe JW, Kahn RL. Successful aging. *Aging (Milano)* 1998;10(2): 142–4.
- [2] Stern PC, Carstensen LL, editors. *The aging mind: opportunities in cognitive research*. Washington, DC: National Academy Press, 2000.
- [3] Unverzagt FW, Gao S, Baiyewu O, Ogunniyi AO, Gureje O, Perkins A, et al. Prevalence of cognitive impairment: Data from the Indianapolis Study of Health and Aging. *Neurology* 2001;57(9):1655–62.
- [4] Scarmeas N, Stern Y. Cognitive reserve: Implications for diagnosis and prevention of Alzheimer's disease. *Curr Neurol Neurosci Rep* 2004;4(5):374–80.
- [5] Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of cognitive training interventions with older adults: A randomized controlled trial. *JAMA* 2002;288(18):2271–81.
- [6] Casel CK. Use It or Lose It Activity may be the best treatment for Aging. *JAMA* 2002;288(18):2333–34.
- [7] Baltes P, Baltes M. *Successful Aging: Perspectives from the Behavioral Sciences*. Cambridge, England: Cambridge University Press, 1990, pp 1–34.
- [8] Blazer DG. Self-efficacy and depression in late life: a primary prevention proposal. *Aging Mental Health* 2002;6(4):315–24.
- [9] Penninx BW, Guralnik JM, Simonsick EM, Kasper JD, Ferrucci L, Fried LP. Emotional vitality among disabled older women: The Women's Health and Aging Study. *J Am Geriatr Soc* 1998;46(7): 807–15.
- [10] Lockenhoff CE, Carstensen LL. Socioemotional selectivity theory, aging, and health: The increasingly delicate balance between regulating emotions and making tough choices. *J Pers* 2004;72(6):1395–424.
- [11] Steffens DC, et al. Perspectives on depression, mild cognitive impairment, and cognitive decline. *Arch Gen Psychiatry* (in press).
- [12] NAMHC. *Mental Health for a Lifetime—Report of the National Advisory Mental Health Council's Workgroup on Aging Research*. Washington, DC: National Institute of Mental Health, 2003.
- [13] Heuser I, Lammers CH. Stress and the brain. *Neurobiol Aging* 2003;24 (Suppl 1): S69–76; discussion S81–2.
- [14] Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M, et al. Executive dysfunction and long-term outcomes of geriatric depression. *Arch Gen Psychiatry* 2000;57(3):285–90.

- [15] Healthy People 2000 Report. PHS/DHHS/National Health Promotion and Disease Prevention, 2000.
- [16] Hall KS, Gao S, Unverzagt FW, Hendrie HC. Low education and childhood rural residence risk for Alzheimer's Disease in African Americans. *Neurology* 2000;54:95–99.
- [17] Manly JJ, Jacobs DM. Future directions in neuropsychological assessment with African Americans. In: Ferraro FR editor. *Minority and cross-cultural aspects of neuropsychological assessment*. Lisse, Netherlands: Swets and Zeitlinger, 2001, p. 79–96.
- [18] Mehta KM, Simonsick EM, Rooks R, Newman AB, Pope SK, Rubin SM et al. Black and white differences in cognitive function test scores: What explains the difference? *J Am Geriatr Soc* 2004;52(12): 2120–7.
- [19] Baumbach GL. Changes in the cerebral circulation in chronic hypertension. Humana Press, 1994, p. 421–31.
- [20] Faraci FM, Heistad DD. Regulation of large cerebral arteries and cerebral microvascular pressure. *Circ Res* 1990;66(1):8–17.
- [21] Nag S. Cerebral changes in chronic hypertension: Combined permeability and immunohistochemical studies. *Acta Neuropathol (Berl)* 1984;62(3):178–84.
- [22] Dufouil C, de Kersaint-Gilly A, Besancon V, Levy C, Auffray E, Brunnereau L, et al. Longitudinal study of blood pressure and white matter hyperintensities: The EVA MRI Cohort. *Neurology* 2001; 56(7):921–6.
- [23] van Dijk EJ, Breteler MM, Schmidt R, Berger K, Nilsson LG, Oudkerk M, et al. The association between blood pressure, hypertension, and cerebral white matter lesions: Cardiovascular determinants of dementia study. *Hypertension* 2004;44(5):625–30.
- [24] Korf ES, White LR, Scheltens P, Launer LJ. Midlife blood pressure and the risk of hippocampal atrophy: The Honolulu Asia Aging Study. *Hypertension* 2004;44(1):29–34.
- [25] Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: The Honolulu-Asia aging study. *Neurobiol Aging* 2000;21(1):49–55.
- [26] Petrovitch H, White LR, Izmirlian G, Ross GW, Havlik RJ, Markesbery W, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: The HAAS. Honolulu-Asia aging Study. *Neurobiol Aging* 2000;21(1):57–62.
- [27] Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med* 2002;162(18):2046–52.
- [28] Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003;163(9):1069–75.
- [29] Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, et al. The Study on COgnition and Prognosis in the Elderly (SCOPE); outcomes in patients not receiving add-on therapy after randomization. *J Hypertens* 2004;22(8):1605–12.
- [30] Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* 1999;53(9):1937–42.
- [31] Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol* 2001;154(7):635–41.
- [32] Kovari E, Gold G, Herrmann FR, Canuto A, Hof PR, Michel JP, et al. Cortical microinfarcts and demyelination significantly affect cognition in brain aging. *Stroke* 2004;35(2):410–4.
- [33] Camus V, Kraehenbuhl H, Preisig M, Bula CJ, Waeber G. Geriatric depression and vascular diseases: What are the links? *J Affect Disord* 2004;81(1):1–16.
- [34] Steffens DC, Krishnan KR. Structural neuroimaging and mood disorders: Recent findings, implications for classification, and future directions. *Biol Psychiatry* 1998;43(10):705–12.
- [35] Thomas AJ, Kalara RN, O'Brien JT. Depression and vascular disease: What is the relationship? *J Affect Disord* 2004;79(1-3):81–95.
- [36] Alexopoulos GS, Meyers BS, Young RC, Mattis S, Kakuma T. The course of geriatric depression with reversible dementia: A controlled study. *Am J Psychiatry* 1993;150(11):1693–9.
- [37] Comijs HC, van Tilburg T, Geerlings SW, Jonker C, Deeg DJ, van Tilburg W, et al. Do severity and duration of depressive symptoms predict cognitive decline in older persons? Results of the Longitudinal Aging Study Amsterdam. *Aging Clin Exp Res* 2004;16(3):226–32.
- [38] Paterniti S, Verdier-Taillefer MH, Dufouil C, Alperovitch A. Depressive symptoms and cognitive decline in elderly people. Longitudinal study. *Br J Psychiatry* 2002;181:406–10.
- [39] Wilson RS, Mendes De Leon CF, Bennett DA, Bienias JL, Evans DA. Depressive symptoms and cognitive decline in a community population of older persons. *J Neurol Neurosurg Psychiatry* 2004;75(1): 126–9.
- [40] Yaffe K, Blackwell T, Gore R, Sands L, Reus V, Browner WS. Depressive symptoms and cognitive decline in nondemented elderly women: a prospective study. *Arch Gen Psychiatry* 1999;56(5):425–30.
- [41] Jorm AF. Is depression a risk factor for dementia or cognitive decline? A review. *Gerontology* 2000;46(4):219–27.
- [42] Palinkas LA, Wingard DL, Barrett-Connor E. Chronic illness and depressive symptoms in the elderly: a population-based study. *J Clin Epidemiol* 1990;43(11):1131–41.
- [43] Penninx BW, Beekman AT, Ormel J, Kriegsman DM, Boeke AJ, van Eijk JT et al. Psychological status among elderly people with chronic diseases: Does type of disease play a part? *J Psychosom Res* 1996; 40(5):521–34.
- [44] Black SA, Goodwin JS, Markides KS. The association between chronic diseases and depressive symptomatology in older Mexican Americans. *J Gerontol A Biol Sci Med Sci* 1998;53(3):M188–94.
- [45] Saunders AM, Hulette O, Welsh-Bohmer KA, Schmechel DE, Crain B, Burke JR, et al. Specificity, sensitivity, and predictive value of apolipoprotein-E genotyping for sporadic Alzheimer's disease. *Lancet* 1996;348(9020):90–3.
- [46] Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* 1997;278(16):1349–56.
- [47] Lee JH, Tang MX, Schupf N, Stern Y, Jacobs DM, Tycko B, et al. Mortality and apolipoprotein E in Hispanic, African-American, and Caucasian elders. *Am J Med Genet* 2001;103(2):121–7.
- [48] Fillenbaum GG, Blazer DG, Burchett BM, Saunders AM, Taylor DH Jr. Apolipoprotein E epsilon4 and risk of mortality in African American and white older community residents. *Gerontologist* 2002;42(3): 381–6.
- [49] Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. Apolipoprotein E polymorphism and cardiovascular disease: A HuGE review. *Am J Epidemiol* 2002;155(6):487–95.
- [50] Wilson PW, Myers RH, Larson MG, Ordovas JM, Wolf PA, Schaefer EJ. Apolipoprotein E alleles, dyslipidemia, and coronary heart disease. The Framingham Offspring Study. *JAMA* 1994;272(21):1666–71.
- [51] National Institute on Aging/Alzheimer's Association Working Group. Apolipoprotein E genotyping in Alzheimer's disease. *Lancet* 1996;347(9008):1091–5.
- [52] Bergeman CS, Plomin R, Pedersen NL, McClearn GE. Genetic mediation of the relationship between social support and psychological well-being. *Psychol Aging* 1991;6(4):640–6.

[53] Jansson M, Gatz M, Berg S, Johansson B, Malmberg B, McClearn GE et al. Gender differences in heritability of depressive symptoms in the elderly. *Psychol Med* 2004;34(3):471–9.

Appendix

Survey Bibliography

- [A1] Aartsen MJ, Smits CH, van Tilburg T, Knipscheer KC, Deeg DJ. Activity in older adults: Cause or consequence of cognitive functioning? A longitudinal study on everyday activities and cognitive performance in older adults. *J Gerontol B Psychol Sci Soc Sci* 2002;57(2):P153–62.
- [A2] Aartsen MJ, Martin M, Zimprich D. Gender differences in level and change in cognitive functioning. Results from the Longitudinal Aging Study Amsterdam. *Gerontology* 2004;50(1):35–8.
- [A3] Abbott RD, White LR, Ross GW, Petrovitch H, Masaki KH, Snowdon DA, et al. Height as a marker of childhood development and late-life cognitive function: The Honolulu-Asia Aging Study. *Pediatrics* 1998;102(3 Pt 1):602–9.
- [A4] Albert MS, Jones K, Savage CR, Berkman L, Seeman T, Blazer D, et al. Predictors of cognitive change in older persons: MacArthur studies of successful aging. *Psychol Aging* 1995;10(4):578–89.
- [A5] Barnes LL, Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA. Gender, cognitive decline, and risk of AD in older persons. *Neurology* 2003;60(11):1777–81.
- [A6] Barnow S, Linden M, Freyberger HJ. The relation between suicidal feelings and mental disorders in the elderly: results from the Berlin Aging Study (BASE). *Psychol Med* 2004;34(4):741–6.
- [A7] Bassuk SS, Glass TA, Berkman LF. Social disengagement and incident cognitive decline in community-dwelling elderly persons. *Ann Intern Med* 1999;131(3):165–73.
- [A8] Beekman AT, MA Bremmer, DJ Deeg, AJ van Balkom, JH Smit, E de Beurs, et al. Anxiety disorders in later life: A report from the Longitudinal Aging Study Amsterdam. *Int J Geriatr Psychiatry* 1998;13(10):717–26.
- [A9] Beekman AT, Deeg DJ, Geerlings SW, Schoevers RA, Smit JH, van Tilburg W. Emergence and persistence of late life depression: A 3-year follow-up of the Longitudinal Aging Study Amsterdam. *J Affect Disord* 2001;65(2):131–8.
- [A10] Bisschop MI, Kriegsman DM, Deeg DJ, Beekman AT, van Tilburg W. The longitudinal relation between chronic diseases and depression in older persons in the community: The Longitudinal Aging Study Amsterdam. *J Clin Epidemiol* 2004;57(2):187–94.
- [A11] Blazer D, Burchett B, Service C, George LK. The association of age and depression among the elderly: An epidemiologic exploration. *J Gerontol* 1991;46(6):M210–5.
- [A12] Blazer DG, Burchett BB, Fillenbaum GG. APOE epsilon4 and low cholesterol as risks for depression in a biracial elderly community sample. *Am J Geriatr Psychiatry* 2002;10(5):515–20.
- [A13] Blazer DG, Fillenbaum GG, Gold DT, Burchett BM, Hays JC. APOE epsilon4 as a predictor of subjective quality of life in a biracial older person community sample. *J Aging Health* 2003;15(4):645–60.
- [A14] Bretsky P, Guralnik JM, Launer L, Albert M, Seeman TE. The role of APOE-epsilon4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. *Neurology* 2003;60(7):1077–81.
- [A15] Carr D. The fulfillment of career dreams at midlife: Does it matter for women's mental health? *J Health Soc Behav* 1997;38(4):331–44.
- [A16] Chyou PH, LR White, K Yano, DS Sharp, CM Burchfiel, R Chen, et al. Pulmonary function measures as predictors and correlates of cognitive functioning in later life. *Am J Epidemiol* 1996;143(8):750–6.
- [A17] Clarke PJ, Marshall V, Ryff CD, Rosenthal CJ. Well-being in Canadian seniors: Findings from the Canadian Study of Health and Aging. *Can J Aging* 2000;19(2):139–59.
- [A18] Comijs HC, Jonker C, Beekman AT, Deeg DJ. The association between depressive symptoms and cognitive decline in community-dwelling elderly persons. *Int J Geriatr Psychiatry* 2001;16(4):361–7.
- [A19] de Beurs E, Beekman AT, Deeg DJ, Van Dyck R, van Tilburg W. Predictors of change in anxiety symptoms of older persons: Results from the Longitudinal Aging Study Amsterdam. *Psychol Med* 2000;30(3):515–27.
- [A20] Dentino AN, Pieper CF, Rao MK, Currie MS, Harris T, Blazer DG, et al. Association of interleukin-6 and other biologic variables with depression in older people living in the community. *J Am Geriatr Soc* 1999;47(1):6–11.
- [A21] Dik MG, Deeg DJ, Bouter LM, Corder EH, Kok A, Jonker C. Stroke and apolipoprotein E epsilon4 are independent risk factors for cognitive decline: A population-based study. *Stroke* 2000;31(10):2431–6.
- [A22] Dik MG, C Jonker, HC Comijs, LM Bouter, JW Twisk, GJ van Kamp et al. Memory complaints and APOE-epsilon4 accelerate cognitive decline in cognitively normal elderly. *Neurology* 2001;57(12):2217–22.
- [A23] Elias MF, D'Agostino RB, Elias PK, Wolf PA. Neuropsychological test performance, cognitive functioning, blood pressure, and age: The Framingham Heart Study. *Exp Aging Res* 1995;21(4):369–91.
- [A24] Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. *Int J Obes Relat Metab Disord* 2003;27(2):260–8.
- [A25] Elias PK, D'Agostino RB, Elias MF, Wolf PA. Blood pressure, hypertension, and age as risk factors for poor cognitive performance. *Exp Aging Res* 1995;21(4):393–417.
- [A26] Elias PK, Elias MF, D'Agostino RB, Silbershatz H, Wolf PA. Alcohol consumption and cognitive performance in the Framingham Heart Study. *Am J Epidemiol* 1999;150(6):580–9.
- [A27] Fillenbaum GG, Landerman LR, Blazer DG, Saunders AM, Harris TB, Launer LJ. The relationship of APOE genotype to cognitive functioning in older African-American and Caucasian community residents. *J Am Geriatr Soc* 2001;49(9):1148–55.
- [A28] Fiske A, Gatz M, Pedersen NL. Depressive symptoms and aging: The effects of illness and non-health-related events. *J Gerontol B Psychol Sci Soc Sci* 2003;58(6):P320–8.
- [A29] Foley D, Monjan A, Masaki K, Ross W, Havlik R, White L, et al. Daytime sleepiness is associated with 3-year incident dementia and cognitive decline in older Japanese-American men. *J Am Geriatr Soc* 2001;49(12):1628–32.
- [A30] Fonda SJ, Herzog AR. Patterns and risk factors of change in somatic and mood symptoms among older adults. *Ann Epidemiol* 2001;11(6):361–8.
- [A31] Galanis DJ, Petrovitch H, Launer LJ, Harris TB, Foley DJ, White LR. Smoking history in middle age and subsequent cognitive performance in elderly Japanese-American men. The Honolulu-Asia Aging Study. *Am J Epidemiol* 1997;145(6):507–15.
- [A32] Galanis DJ, Joseph C, Masaki KH, Petrovitch H, Ross GW, White L. A longitudinal study of drinking and cognitive performance in elderly Japanese American men: The Honolulu-Asia Aging Study. *Am J Public Health* 2000;90(8):1254–9.
- [A33] Gates GA, Cobb JL, Linn RT, Rees T, Wolf PA, D'Agostino RB. Central auditory dysfunction, cognitive dysfunction, and dementia in older people. *Arch Otolaryngol Head Neck Surg* 1996;122(2):161–7.
- [A34] Geerlings MI, Schoevers RA, Beekman AT, Jonker C, Deeg DJ, Schmand B, et al. Depression and risk of cognitive decline and

- Alzheimer's disease. Results of two prospective community-based studies in The Netherlands. *Br J Psychiatry* 2000;176:568–75.
- [A35] Glass TA, Kasl SV, Berkman LF. Stressful life events and depressive symptoms among the elderly. Evidence from a prospective community study. *J Aging Health* 1997;9(1):70–89.
- [A36] Glynn RJ, Beckett LA, Hebert LE, Morris MC, Scherr PA, Evans DA. Current and remote blood pressure and cognitive decline. *JAMA* 1999;281(5):438–45.
- [A37] Graves AB, Rajaram L, Bowen JD, McCormick WC, McCurry SM, Larson EB. Cognitive decline and Japanese culture in a cohort of older Japanese Americans in King County, WA: The Kame Project. *J Gerontol B Psychol Sci Soc Sci* 1999;54(3):S154–61.
- [A38] Graves AB, Bowen JD, Rajaram L, McCormick WC, McCurry SM, Schellenberg GD, Larson EB. Impaired olfaction as a marker for cognitive decline: Interaction with apolipoprotein E epsilon4 status. *Neurology* 1999;53(7):1480–7.
- [A39] Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KM, et al. Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 2000;160(2):174–80.
- [A40] Grodstein F, Chen J, Pollen DA, Albert MS, Wilson RS, Folstein MF, et al. Postmenopausal hormone therapy and cognitive function in healthy older women. *J Am Geriatr Soc* 2000;48(7):746–52.
- [A41] Grodstein F, J Chen, RS Wilson, JE Manson Type 2 diabetes and cognitive function in community-dwelling elderly women. *Diabetes Care* 2001;24(6):1060–5.
- [A42] Grodstein F, Chen J, Willett WC. High-dose antioxidant supplements and cognitive function in community-dwelling elderly women. *Am J Clin Nutr* 2003;77(4):975–84.
- [A43] Grodstein F, Chen J, Hankinson SE. Cataract extraction and cognitive function in older women. *Epidemiology* 2003;14(4):493–7.
- [A44] Guo Z, Fratiglioni L, Winblad B, Viitanen M. Blood pressure and performance on the Mini-Mental State Examination in the very old. Cross-sectional and longitudinal data from the Kungsholmen Project. *Am J Epidemiol* 1997;145(12):1106–13.
- [A45] Haan MN, Shemanski L, Jagust WJ, Manolio TA, Kuller L. The role of APOE epsilon4 in modulating effects of other risk factors for cognitive decline in elderly persons. *JAMA* 1999;282(1): 40–6.
- [A46] Hybels CF, Blazer DG, Pieper CF. Toward a threshold for sub-threshold depression: an analysis of correlates of depression by severity of symptoms using data from an elderly community sample. *Gerontologist* 2001;41(3):357–65.
- [A47] Isaacowitz DM, J Smith. Positive and negative affect in very old age. *J Gerontol B Psychol Sci Soc Sci* 2003;58(3):P143–52.
- [A48] Jonker C, Comijs HC, Smit JH. Does aspirin or other NSAIDs reduce the risk of cognitive decline in elderly persons? Results from a population-based study. *Neurobiol Aging* 2003;24(4):583–8.
- [A49] Kalmijn S, Launer LJ, Lindemans J, Bots ML, Hofman A, Breteler MM. Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam Study. *Am J Epidemiol* 1999;150(3):283–9.
- [A50] Kang JH, Grodstein F. Regular use of nonsteroidal anti-inflammatory drugs and cognitive function in aging women. *Neurology* 2003;60(10):1591–7.
- [A51] Kramer SE, Kapteyn TS, Kuik DJ, Deeg DJ. The association of hearing impairment and chronic diseases with psychosocial health status in older age. *J Aging Health* 2002;14(1):122–37.
- [A52] Kuller LH, Shemanski L, Manolio T, Haan M, Fried L, Bryan N, et al. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. *Stroke* 1998;29(2):388–98.
- [A53] Kunzmann U, Little TD, Smith J. Is age-related stability of subjective well-being a paradox? Cross-sectional and longitudinal evidence from the Berlin Aging Study. *Psychol Aging* 2000;15(3): 511–26.
- [A54] Kunzmann U, Little T, Smith J. Perceiving control: A double-edged sword in old age. *J Gerontol B Psychol Sci Soc Sci* 2002;57(6): P484–91.
- [A55] Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA* 1995; 274(23):1846–51.
- [A56] Lee S, Kawachi I, Berkman LF, Grodstein F. Education, other socioeconomic indicators, and cognitive function. *Am J Epidemiol* 2003;157(8):712–20.
- [A57] Lee S, Kawachi I, Grodstein F. Does caregiving stress affect cognitive function in older women? *J Nerv Ment Dis* 2004;192(1): 51–7.
- [A58] Logroscino G, Kang JH, Grodstein F. Prospective study of type 2 diabetes and cognitive decline in women aged 70–81 years. *BMJ* 2004;328(7439):548.
- [A59] Lui LY, Stone K, Cauley JA, Hillier T, Yaffe K. Bone loss predicts subsequent cognitive decline in older women: the study of osteoporotic fractures. *J Am Geriatr Soc* 2003;51(1):38–43.
- [A60] Masaki KH, Losonczy KG, Izmirlian G, Foley DJ, Ross GW, Petrovitch H, et al. Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. *Neurology* 2000;54(6):1265–72.
- [A61] Matthews K, Cauley J, Yaffe K, Zmuda JM. Estrogen replacement therapy and cognitive decline in older community women. *J Am Geriatr Soc* 1999;47(5):518–23.
- [A62] Mehta KM, Simonsick EM, Penninx BW, Schulz R, Rubin SM, Satterfield S, et al. Prevalence and correlates of anxiety symptoms in well-functioning older adults: findings from the health aging and body composition study. *J Am Geriatr Soc* 2003;51(4):499–504.
- [A63] Meyer PM, Powell LH, Wilson RS, Everson-Rose SA, Kravitz HM, Luborsky JL, et al. A population-based longitudinal study of cognitive functioning in the menopausal transition. *Neurology* 2003; 61(6):801–6.
- [A64] Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS. Dietary fat intake and 6-year cognitive change in an older biracial community population. *Neurology* 2004;62(9):1573–9.
- [A65] Ostbye T, Steenhuis R, Walton R, Cairney J. Correlates of dysphoria in Canadian seniors: The Canadian Study of Health and Aging. *Can J Public Health* 2000;91(4):313–7.
- [A66] Ott A, K Andersen, ME Dewey, L Letenneur, C Brayne, JR Copeland, et al. Effect of smoking on global cognitive function in nondemented elderly. *Neurology* 2004;62(6):920–4.
- [A67] Peila R, White LR, Petrovich H, Masaki K, Ross GW, Havlik RJ, et al. Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive impairment: the Honolulu-Asia aging study. *Stroke* 2001;32(12):2882–9.
- [A68] Penninx BW, Kritchevsky SB, Yaffe K, Newman AB, Simonsick EM, Rubin S, et al. Inflammatory markers and depressed mood in older persons: Results from the Health, Aging and Body Composition study. *Biol Psychiatry* 2003;54(5):566–72.
- [A69] Petrovitch H, White L, Masaki KH, Ross GW, Abbott RD, Rodriguez BL, et al. Influence of myocardial infarction, coronary artery bypass surgery, and stroke on cognitive impairment in late life. *Am J Cardiol* 1998;81(8):1017–21.
- [A70] Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, Manson JE, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial. *JAMA* 2003;289(20):2663–72.
- [A71] Rice MM, Graves AB, McCurry SM, Gibbons LE, Bowen JD, McCormick WC, et al. Postmenopausal estrogen and estrogen-progestin use and 2-year rate of cognitive change in a cohort of older Japanese American women: The Kame Project. *Arch Intern Med* 2000;160(11):1641–9.

- [A72] Rozzini R, Ferrucci L, Losonczy K, Havlik RJ, Guralnik JM. Protective effect of chronic NSAID use on cognitive decline in older persons. *J Am Geriatr Soc* 1996;44(9):1025–9.
- [A73] Schmand B, Smit J, Lindeboom J, Smits C, Hooijer C, Jonker C, Deelman B. Low education is a genuine risk factor for accelerated memory decline and dementia. *J Clin Epidemiol* 1997;50(9):1025–33.
- [A74] Schoevers RA, Beekman AT, Deeg DJ, Geerlings MI, Jonker C, Van Tilburg W. Risk factors for depression in later life; results of a prospective community based study (AMSTEL). *J Affect Disord* 2000;59(2):127–37.
- [A75] Schwartz BS, Stewart WF, Bolla KI, Simon PD, Bandeen-Roche K, Gordon PB, et al. Past adult lead exposure is associated with longitudinal decline in cognitive function. *Neurology* 2000;55(8):1144–50.
- [A76] Seeman T, McAvay G, Merrill S, Albert M, Rodin J. Self-efficacy beliefs and change in cognitive performance: MacArthur Studies of Successful Aging. *Psychol Aging* 1996;11(3):538–51.
- [A77] Seeman TE, Lusignolo TM, Albert M, Berkman L. Social relationships, social support, and patterns of cognitive aging in healthy, high-functioning older adults: MacArthur studies of successful aging. *Health Psychol* 2001;20(4):243–55.
- [A78] Slooter AJ, van Duijn CM, Bots ML, Ott A, Breteler MB, De Voucht J, et al. Apolipoprotein E genotype, atherosclerosis, and cognitive decline: The Rotterdam Study. *J Neural Transm Suppl* 1998;53:17–29.
- [A79] Tiemeier H, van Tuijl HR, Hofman A, Meijer J, Kiliaan AJ, Breteler MM. Vitamin B12, folate, and homocysteine in depression: the Rotterdam Study. *Am J Psychiatry* 2002;159(12):2099–101.
- [A80] Tiemeier H, Bakker SL, Hofman A, Koudstaal PJ, Breteler MM. Cerebral haemodynamics and depression in the elderly. *J Neurol Neurosurg Psychiatry* 2002;73(1):34–9.
- [A81] Tiemeier H, Breteler MM, van Popele NM, Hofman A, Witteman JC. Late-life depression is associated with arterial stiffness: a population-based study. *J Am Geriatr Soc* 2003;51(8):1105–10.
- [A82] Tiemeier H, Hofman A, van Tuijl HR, Kiliaan AJ, Meijer J, Breteler MM. Inflammatory proteins and depression in the elderly. *Epidemiology* 2003;14(1):103–7.
- [A83] Tiemeier H, van Dijk W, Hofman A, Witteman JC, Stijnen T, Breteler MM. Relationship between atherosclerosis and late-life depression: the Rotterdam Study. *Arch Gen Psychiatry* 2004;61(4):369–76.
- [A84] van den Heuvel N, Smits CH, Deeg DJ, Beekman AT. Personality: A moderator of the relation between cognitive functioning and depression in adults aged 55–85? *J Affect Disord* 1996;41(3):229–40.
- [A85] Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 2003;348(13):1215–22.
- [A86] White L, Katzman R, Losonczy K, Salive M, Wallace R, Berkman L, et al. Association of education with incidence of cognitive impairment in three established populations for epidemiologic studies of the elderly. *J Clin Epidemiol* 1994;47(4):363–74.
- [A87] Whooley MA, Grady D, Cauley JA. Postmenopausal estrogen therapy and depressive symptoms in older women. *J Gen Intern Med* 2000;15(8):535–41.
- [A88] Winnock M, Letenneur L, Jacqmin-Gadda H, Dallongeville J, Amouyel P, Dartigues JF. Longitudinal analysis of the effect of apolipoprotein E epsilon4 and education on cognitive performance in elderly subjects: the PAQUID study. *J Neurol Neurosurg Psychiatry* 2002;72(6):794–7.
- [A89] Yaffe K, Cauley J, Sands L, Browner W. Apolipoprotein E phenotype and cognitive decline in a prospective study of elderly community women. *Arch Neurol* 1997;54(9):1110–4.
- [A90] Yaffe K, Grady D, Pressman A, Cummings S. Serum estrogen levels, cognitive performance, and risk of cognitive decline in older community women. *J Am Geriatr Soc* 1998;46(7):816–21.
- [A91] Yaffe K, Browner W, Cauley J, Launer L, Harris T. Association between bone mineral density and cognitive decline in older women. *J Am Geriatr Soc* 1999;47(10):1176–82.
- [A92] Yaffe K, Haan M, Byers A, Tangen C, Kuller L. Estrogen use, APOE, and cognitive decline: evidence of gene-environment interaction. *Neurology* 2000;54(10):1949–54.
- [A93] Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: women who walk. *Arch Intern Med* 2001;161(14):1703–8.
- [A94] Yaffe K, Barrett-Connor E, Lin F, Grady D. Serum lipoprotein levels, statin use, and cognitive function in older women. *Arch Neurol* 2002;59(3):378–84.
- [A95] Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology* 2003; 61(1):76–80.
- [A96] Yip AG, Brayne C, Easton D, Rubinsztein DC. Apolipoprotein E4 is only a weak predictor of dementia and cognitive decline in the general population. *J Med Genet* 2002;39(9):639–43.