Cognitive and Physical Disabilities and Aging-Related Complications of Diabetes

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Diabetes has gained notoriety as a major chronic disease epidemic in the United States[1–4] and is threatening to undo some of the success in coronary heart disease (CHD) and stroke mortality prevention made during the past several decades.[5] An increase in the prevalence of type 2 diabetes among youth has been a particularly alarming aspect of this epidemic,[6] but the diabetes epidemic in developed countries affects the entire age range, and the greatest absolute increase and total numbers of diabetes cases are actually occurring among the elderly.[1–4,7] Currently, 42% of the diabetic population in the United States is 65 years old or older; this proportion is projected to increase to 53% by 2025 and to 58% by 2050.[7]

The increase in diabetes among the elderly is concerning because, in addition to the wide range of traditional diabetes complications (including acute hyperglycemic and hypoglycemic events and vascular complications that may lead to vision loss, renal failure, foot ulcers and amputation, myocardial infarction, stroke, and cardiovascular death),[4,8] evidence has been growing that diabetes is associated with increased risk of cognitive decline, physical disability, falls and fractures, and other conditions associated with geriatric syndromes.[9,10] These less traditional complications are common and may be as damaging as the commonly recognized vascular outcomes of the disease to older diabetic people because of their direct influence on quality of life. Indeed, for older people with diabetes, the threat of loss of independence due to progressing cognitive and physical decline may be of greater direct concern than the clinical progression of diabetes complications.

Unfortunately, few epidemiological studies have examined the impact of diabetes on functional outcomes, and almost no randomized clinical trials (RCTs) have examined the effect of treatments on these outcomes. In this review, we summarize the research associating diabetes with these aging-related outcomes and comment on the potential for clinical and public health interventions to reduce the burden of these outcomes among elderly people with diabetes.

Associations Between Diabetes and Cognitive Decline or Dementia

Numerous cross-sectional and case-control studies dating back to the 1980s have shown positive associations between diabetes and cognitive impairment.[11–13] Many overlapping mechanisms for this association have been proposed. Chronic hyperglycemia and the production of advanced glycated end products may damage vascular tissue and endothelial function, DNA, and mitochondria in the brain and increase free radicals, inflammatory responses, and amyloid deposition.[11–13] Chronic hyperglycemia may also influence cerebral blood flow, neurotransmitter function, or nutrient delivery to the brain. In addition, diabetes could influence cognitive function by leading to cardiovascular events, transient ischemic attacks, and strokes. Repeated hypoglycemic events and related metabolic and vascular disruption might influence long-term cognitive function. Diabetes may also be a marker of other factors, such as insulin resistance and hypertension, or may represent a common genetic susceptibility to both diabetes and Alzheimer's disease dementia.[11–13]

Regardless of the mechanism, several large prospective studies have associated diabetes with cognitive decline and clinical dementia during the past 5 years. Four found a significant association between diabetes and rate of cognitive decline as measured by cognitive tests over 4–6 years.[14–17] Two of these studies found a 60–100% greater risk of cognitive decline among people with diabetes than among those without diabetes.[15,16] Associations were observed for a range of cognitive domains, including attention, concentration, visuo-spatial reasoning, memory, and psychomotor speed, but tended to not be associated with decline on the modified mini-mental state exam.

IN BRIEF

As older adults make up an increasingly larger portion of the diabetic population, the spectrum of diabetes complications will likely expand. In addition to the traditional vascular complications, diabetes has been associated with excess risk for cognitive and physical decline, falls, fractures, and depression. These complications, which are common and can profoundly affect quality of life, will challenge clinicians, health care systems, and public health organizations to identify effective ways of optimizing quality of life among older adults with diabetes.

Two earlier studies failed to find any association between diabetes and change in cognitive function. However, the first study had limited power,[18] and the second study used only the mini-mental state exam, a screening test with high specificity but poor sensitivity, to study change in cognitive function.[19]

Recent studies have also addressed the effect of diabetes on clinically defined dementia. The findings have varied depending on the type of dementia. At least three studies have found diabetes to have a 50–200% greater risk for overall dementia and Alzheimer's disease.[20–23] Other studies have found diabetes associated with about twice the risk of vascular dementia but not of Alzheimer's disease.[24–26] The study by Luchsinger et al.[25] found that diabetes was particularly associated with stroke-mediated dementia, wherein the relative risk was >3.

Although no formal quantitative meta-analyses have been conducted on this issue, these studies suggest that diabetes is associated with both subtle declines in cognitive function (as measured by neuropsychological tests) and more profound declines in function (as assessed by clinical dementia criteria). Associations with Alzheimer's disease appear relatively weak, indicating that the association with dementia is driven by vascular factors. Separation of vascular dementia from Alzheimer's disease dementia remains difficult, however, especially because Alzheimer's disease may be influenced by vascular factors.[27,28]

On the whole, these studies lacked data to determine the specific mechanisms underlying the association between diabetes and cognitive decline or dementia. Similarly, it is unknown whether aspects of metabolic and cardiovascular risk control among people with diabetes play any role in increasing the risk of cognitive impairment and decline.

Associations Between Diabetes and Physical Disability or Functional Status

Levels of disability, assessed according to difficulty with mobility, walking, and carrying out complex and simple daily activities, have emerged as key indicators of morbidity for older adults.[29,30] For an individual, measures of disability and independence are directly influenced by the number and severity of chronic diseases present and are central components of quality of life. At the population level, disability measures are key indicators of overall health status and whether improved medical care and longevity are accompanied by reduced morbidity.

Although there are many reasons to suspect that diabetes could lead to increased physical disability, the magnitude or key factors explaining such a relationship have rarely been examined. In the Third National Health and Nutrition Examination Survey (NHANES III), women and men aged ≥60 years with diagnosed diabetes were ~2–3 times more likely to be unable to walk one-fourth of a mile, climb stairs, and do housework than similar-aged adults without diabetes.[31] Women with diabetes also had significantly slower walking speed, worse balance, and a 58% higher likelihood of falling than did nondiabetic women. In a prospective study of women in the Study of Osteoporotic Fractures,[32] women with diabetes had twice the yearly incidence of becoming unable to walk one-fourth of a mile (4.3 vs. 1.9% among nondiabetic women), doing heavy housework (8.5 vs. 4%), or preparing meals (1.5 vs. 0.7%). Recent analyses from the Women's Health and Aging Study have found similar degrees of association between diabetes and mobility problems, activities of daily living disabilities, and balance among a cohort of older women at high risk for disability.[33,34]

The mechanisms explaining the association between diabetes and physical disability are probably multifactorial. In NHANES III, CHD and high body mass index (BMI) were the strongest explanatory factors among women, accounting for 52% of their excess risk for disability.[31] Among men, CHD and stroke were the most important explanatory factors, explaining 25 and 21% of the excess disability risk, respectively. In the Study of Osteoporotic Fractures, age, CHD, arthritis, physical inactivity, BMI, and visual impairment were key predictors of disability among the women with diabetes.[32] And in the Women's Health and Aging Study,[34] where more information on lower-extremity disease was collected, peripheral nerve dysfunction, peripheral arterial disease, and depression were the main predictors of physical disability. In each of these studies, however, a significant excess risk of disability associated with diabetes remained, even after controlling for diabetes-related complications. This indicates either that diabetes has an intrinsic influence on disability or that other unmeasured or undiscovered diabetes-related complications influence the risk for disability.

The effects of diabetes on physical disability may extend to other adverse aging-related outcomes. At least four large studies have found an increased risk of falling among older adults with type 2 diabetes.[35–38] Schwartz et al.[35] found that, although women with type 2 diabetes had a significantly higher bone mineral density than did nondiabetic women, the increased risk of falls (53% greater risk of at least one fall per year) apparently outweighed this advantage, resulting in a 49% increased risk of fractures. Other studies have supported this finding, indicating that women with diabetes may be at particularly increased risk of hip or foot fractures.[39–42]

Interventions to Reduce Cognitive and Functional Decline

As a result of numerous large RCTs conducted during the past decade, clinicians are now armed with the knowledge that aggressive management of glycemia, blood pressure, and lipids; aspirin use; smoking cessation; and regular screening for foot, eye, and kidney problems may prevent and delay the complications of diabetes.[43] Some of these and other interventions might also influence the risk for aging-related diabetes outcomes, such as cognitive and physical disabilities. Unfortunately, most

large effectiveness studies were conducted among middle-aged populations, and almost no RCTs examined the effect of interventions on cognitive or functional decline.

Management of glycemia and blood pressure could conceivably ameliorate cognitive decline among patients with diabetes. Two short-term, nonrandomized studies suggested that improved glycemic control improves cognitive function over 3–6 months.[44,45] Another study found that people who received intensive inpatient management had improved concentration and psychomotor function compared to patients who received regular home-based care, but the two groups did not differ in glycated hemoglobin concentration, making it unclear which aspect of care influenced cognitive function.[46] An RCT of more than 500 men and women with type 2 diabetes showed that glycemic management over 12 weeks was associated with improvement in several acute symptoms, as well as subjectively reported confusion and cognitive function.[47] Finally, the Diabetes Control and Complications Trial found no difference in change in overall cognitive function between younger people with type 1 diabetes randomized to intensive glycemic management versus regular care. Thus, although glycemic control remains a possible approach to prevent or reduce cognitive decline, the lack of long-term RCTs in older diabetic populations makes it unclear whether such benefits are likely to occur.[48]

Several studies have examined the effects of antihypertensive use on cognitive function as part of large RCTs examining cardiovascular disease outcomes.[49–51] Two of these studies found no effect of antihypertensive treatment on the rate of cognitive decline,[49,50] but another, the Systolic Hypertension in Europe trial,[51] found a 50% reduction in the incidence of dementia among treated hypertensive adults aged ≥60 years after 2 years of follow-up. In a further analysis (median follow-up 3.9 years), patients originally randomized to combination antihypertensive treatment using calcium-channel blockers had a net 7.0/3.2 mmHg lower blood pressure and a 55% lower incidence of dementia than did control subjects.[52] Treatment-related reductions were greater for Alzheimer's dementia (62%) than for mixed or vascular dementia (48%). The treatment group also had a lower rate of disability measured by difficulty carrying out activities of daily living. None of these analyses were conducted primarily among people with diabetes.

For patients with Alzheimer's disease, cholinesterase inhibitors and vitamin E supplements have emerged as standards of care. In addition, clinical research is actively underway examining the long-term effects of these drugs and is exploring the effects of anti-inflammatory drugs and agents aimed at blocking and clearing amyloid plaques.[53]

Several potential interventions could reduce the risk of physical disability, but none have been tested in RCTs among older diabetic people. In recent observational studies of diabetic adults, physical inactivity, obesity, depression, CHD, lower-extremity disease, and arthritis were identified as factors associated with physical disability. Structured exercise programs involving walking and strength and balance training have been associated with improved functional status and reduced incidence of disability among older adults.[54,55] Weight loss has also been associated with improved physical function in obese people,[56] but it is unclear whether weight loss is likely to improve long-term outcomes among obese older people with diabetes.[57]

Barriers to Primary Care Management

Although the clinical goals and guidelines for people with diabetes are similar for older and younger adults, several factors make the care of older diabetic patients particularly complex. The functional status of older people with diabetes is more heterogeneous than that of younger people because the older population ranges from people with newly diagnosed diabetes to those with decades of poorly controlled diabetes. Some older people have few or no comorbid conditions, whereas others have years of diabetes-related complications.

Similarly, life expectancies vary considerably, which means that different interventions may have different value for different patients depending on their anticipated effect on quality of life. For frail older adults with diabetes who have a short life expectancy, substantial comorbidity, or significant difficulty adhering to treatment recommendations, aggressive targets for blood pressure, lipids, or glucose levels may not be appropriate or attainable. Moreover, aggressive management of these conditions may not provide the same benefit as observed for younger people and can instead result in harm, such as episodes of hypoglycemia or hypotension. The goals of therapy might instead be to enhance quality of life through less aggressive targets aimed at reducing and managing bothersome symptoms.

Polypharmacy is common among the elderly because of the desire to simultaneously manage glycemia, hyperlipidemia, hypertension, and other associated conditions. Yet polypharmacy can affect cognitive ability, physical functioning, and depression through drug-drug or drug-disease interactions. The use of medications, particularly those with sedating effects, is a risk factor for falls[58] and cognitive impairment.[59,60] Other medications have been associated with urinary incontinence,[61] depression,[62] and failure to thrive.[63] One RCT found that withdrawal of psychotropic medications significantly reduced the risk of falling.[64] For these reasons, it is important for clinicians to carefully review medications, have a clear rationale for why each medication is indicated, consider costs and dosing schedules when prescribing medications (once-daily dosing is generally preferred), and discuss the benefits and potential side effects of each medication

with elderly patients and their family members or caregivers.

Depression is more common among people with diabetes than without it[65,66] and may be a key mediator of the association between diabetes and cognitive or physical decline. Depression is also likely to impede diabetes self-management and to increase the risk for diabetes-related morbidity and death.[67] Older adults have high rates of underdiagnosis and undertreatment of their depressive symptoms, and <10% of depressed older adults and <5% of older adults with high levels of depressive symptoms receive antidepressant medications.[68,69] Evidence from two carefully conducted meta-analyses of RCTs revealed that pharmacological or psychological treatment of older adults (age >55 years) is effective in reducing depressive symptoms,[70,71] and a systematic review of RCTs found similar findings among physically ill people.[72]

Data on the relationship between screening for depression in the clinical setting and patient outcomes are mixed, however. One RCT found that middle-aged patients screened with a single question or a longer survey were significantly more likely to recover from depression than were patients not screened for depression, but mean improvement in depressive symptoms was not significantly different from the control group.[73] Another partially RCT found no improvement in depression among patients aged ≥70 years who were screened by office staff before their initial visit.[74]

Summary and Future Needs

The high cumulative incidence of cognitive decline, physical decline, and related geriatric syndromes among older diabetic adults indicates the need for more focused attention on clinical and public health approaches to reduce this burden. Inclusion of older segments of the population and measurement of functional outcomes in major diabetes intervention studies is a major step in this direction. Development of guidelines specific to the management of older patients with diabetes may also help reduce some of their functional decline.

Among the unanswered questions that warrant examination are when and how to prioritize interventions targeting blood pressure, glycemia, elevated lipids, and aspirin use and how to stratify older adults by their likelihood of risk or benefit from intensive therapies. The heterogeneity of older people with diabetes may mean that interventions that address screening, prevention, or treatment of age-associated syndromes such as cognitive or functional decline, depression, and disability may enhance diabetes management.

Finally, office-based and system-level approaches could improve long-term functioning of older people. These approaches include screening for dementia, impaired physical functioning, depression, and frailty to help focus treatment approaches, identify preventable causes, and better organize caregivers. Broader system-based approaches include case management, home geriatric assessment, and disease management programs. Systematic research into the effectiveness of these varied approaches will help prioritize their use and facilitate implementation in the form of public health policy.

REFERENCES

[1]An American epidemic: diabetes. *Newsweek* September 4, 2000, p. 40–46

[2]Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM, Byrd-Holt DD: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Examination Survey, 1988–1994. *Diabetes Care* 21:518–524, 1998

[3]Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS: Diabetes trends in the U.S., 1990–1998. *Diabetes Care* 23:1278–1283, 2000

[4]Geiss L (Ed). *Diabetes Surveillance, 1997.* Atlanta, Ga., U.S. Department of Health and Human Services, 1997

[5]Centers for Disease Control and Prevention: Decline in deaths from heart disease and stroke: United States, 1900–1999. *Morb Mortal Wkly Rep* 48:649–656, 1999

[6]Fagot-Campagna A, Pettitt DJ, Engelgau MM, Rios Burrows N, Geiss LS, Valdez R, Beckles G, Saaddine J, Gregg EW, Williamson DF, Narayan KMV: Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 136:664–672, 2000

[7]Boyle JP, Honeycutt AA, Narayan KM, Hoerger TJ, Geiss LS, Chen H, Thompson TJ: Impact of changing demography and disease prevalence in the U.S. *Diabetes Care* 24:1936–1940, 2001

[8]Nathan DM: Long-term complications of diabetes mellitus. *N Engl J Med* 328:1676–1685, 1993

[9]Gregg EW, Engelgau ME, Narayan KMV: Cognitive decline, physical disability, and other unappreciated outcomes of diabetes and aging (Editorial). *BMJ* 325:916–917, 2002

[10]Strachan MWJ, Frier BM, Deary IJ: Type 2 diabetes and cognitive impairment. *Diabet Med* 20:1–2, 2003

[11]Richardson JTE: Cognitive function in diabetes mellitus. *Neurosci Biobehav Rev* 14:385–388, 1990

[12]Strachan MWJ, Deary IJ, Ewing FME, Friere BM: Is type II diabetes associated with an increased risk of cognitive dysfunction? *Diabetes Care* 20:438–445, 1997

[13]Stewart R, Liolitsa D: Type 2 diabetes mellitus, cognitive impairment and dementia. *Diabet Med* 16:93–112, 1999

[14]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* 282:40–46, 1999

[15]Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KMV, Cummings SR: Is diabetes associated with cognitive impairment and cognitive decline among older women? *Arch Intern Med* 160:174–180, 2000

[16]Fontbonne A, Berr C, Ducimetiere P, Alperovitch A: Changes in cognitive abilities over a 4-year period are unfavorably affected in elderly diabetic subjects: results of the Epidemiology of Vascular Aging Study. *Diabetes Care* 24:366–370, 2001

[17]Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR: Cardiovascular risk factors and cognitive decline in middle-aged adults. *Neurology* 56:42–48, 2001

[18]Robertson-Tchabo EA, Arenberg D, Tobin JD, Plotz JB: A longitudinal study of cognitive performance in noninsulin dependent (type II) diabetic men. *Exp Gerontol* 21:459–467, 1986

[19]Kalmijn S, Feskens EJM, Launer LJ, Stijnen T, Kromhout D: Glucose intolerance, hyperinsulinemia and cognitive function in a general population of elderly men. *Diabetologia* 38:1096–1102, 1995

[20]Yoshitake T, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Nomiyama K, Kawano H, Ueda K: Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. *Neurology* 45:1161–1168, 1995

[21]Leibson CK, Rocca WA, Hanson VA, Cha R, Kokmen E, O'Brien PC, Palumbo PJ: The risk of dementia among persons with diabetes melli-

tus: a population-based cohort study. *Am J Epidemiol* 145:301–308, 1997

[22]Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM: Diabetes mellitus and the risk of dementia: the Rotterdam Study. *Neurology* 53:1937–1942, 1999

[23]Peila R, Rodriguez BL, Launer LJ: Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies. *Diabetes* 51:1256–1262, 2002

[24]Katzman R, Aronson M, Fuld P, Kawas C, Brown T, Morgenstern H, Frishman W, Gidez L, Eder H, Ooi WL: Development of dementing illnesses in an 80-year-old volunteer cohort. *Ann Neurol* 25:317–324, 1989

[25]Luchsinger JA, Tang M, 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* 154:635–641, 2001

[26]MacKnight C, Rockwood K, Awalt E, McDowell I: Diabetes mellitus and risk of dementia, Alzheimer's disease and vascular cogntive impairment in the Canadian Study of Health and Aging. *Dement Geriatr Cogn Disord* 14:77–83, 2002

[27]Kivepelto M, Helkala E, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissien A: Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 322:1447–1451, 2001

[28]Launer LJ: Demonstrating the case that AD is a vascular disease: epidemiologic evidence. *Ageing Res Rev* 1:61–77, 2002

[29]Fried LP: Epidemiology of aging. *Epidemiol Rev* 22:95–106, 2000

[30]Guralnik JM, Fried LP, Salive ME: Disability as a public health outcome in the aging population. *Annu Rev Public Health* 17:25–46, 1996

[31]Gregg EW, Beckles GL, Williamson DF, Leveille SG, Langlois JA, Engelgau MM, Narayan KM: Diabetes and physical disability among U.S. adults. *Diabetes Care* 23:1272–1277, 2000

[32]Gregg EW, Mangione CM, Cauley JA, Thompson TJ, Schwartz AV, Ensrud KE, Nevitt MC: Diabetes and incidence of functional disability in older women. *Diabetes Care* 25:61–67, 2002

[33]Volpato S, Ferrucci L, Blaum C, Ostir G, Cappola A, Fried LP, Fellin R, Guralnik JM: Progression of lower-extremity disability in older women with diabetes. *Diabetes Care* 26:70–75, 2001

[34]Volpato S, Blaum C, Resnick H, Ferrucci L, Fried LP, Guralnik JM: Comorbidities and impairments explaining the association between diabetes and lower extremity disability. *Diabetes Care* 25:678–683, 2002

[35]Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg EW, Ensurd KE, Schreiner PJ, Margolis KL, Cauley JA, Nevitt MC, Black DM, Cummings SR: Older women with diabetes have a higher risk of falls: a prospective study. *Diabetes Care* 25:1749–1754, 2002

[36]Malmivaara A, Heliovaara M, Knekt P, Reunanen A, Aromaa A: Risk factors for injurious falls leading to hospitalization or death in a cohort of 19,500 adults. *Am J Epidemiol* 138:384–394, 1994

[37]Miller DK, Lui LY, Perry HM, Kaiser FE, Morley JE: Reported and measured physical functioning in older inner-city diabetic African-Americans. *J Gerontol Biol Sci Med Sci* 54:M230–M236, 1999

[38]Schwartz AV, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Jamal SA, Black DM, Cummings SR: Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab* 86:32–38, 2001

[39]Meyer HE, Tverdal A, Falch JA: Risk factors for hip fracture in middle-aged Norwegian women and men. *Am J Epidemiol* 137:1203–1211, 1993

[40]Seeley DG, Kelsey J, Jergas M, Nevitt MC: Predictors of ankle and foot fractures in older women. *Am J Epidemiol* 135:477–489, 1996

[41]Forsen L, Meyer HE, Midthjell K, Edna TH: Diabetes mellitus and the incidence of hip fracture: results from the Nord-Trondelag Health Survey. *Diabetologia* 42:920–925, 1999

[42]Ottenbacher KJ, Ostir GV, Peek MK, Goodwin JS, Markides KS: Diabetes mellitus as a risk factor for hip fracture in Mexican American older adults. *J Gerontol Biol Med Sci* 57:M648–M653, 2002

[43]Narayan KMV, Gregg EW, Fagot-Campagna A, Engelgau MM, Vinicor F: Diabetes: a common, growing, serious, costly, and potentially preventable public health problem. *Diabetes Res Clin Pract* 50 (Suppl. 2):77–84, 2000

[44]Gradman TJ, Laws A, Thompson LW, Reaven GM: Verbal learning and/or memory improves with glycemic control in older subjects with non-insulin-dependent diabetes mellitus. *J Am Geriatr Soc* 41:1305–1312, 1993

[45]Meneilly GS, Cheung E, Tessier D, Yakura C, Tuokko H: The effect of improved glycemic control on cognitive functions in the elderly patient with diabetes. *J Gerontol A Biol Med Sci* 48:M117–M121, 1993

[46]Naor M, Steingruber HJ, Westhoff K, Schottenfeld-Naor Y, Gries AF: Cognitive function in elderly non-insulin-dependent diabetic patients before and after inpatient treatment for metabolic control. *J Diabetes Complications* 11:40–46, 1997

[47]Testa MA, Simonson DC: Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. *JAMA* 280:1490–1496, 1998

[48]The DCCT Research Group: Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Intern Med* 124:379–388, 1996

[49]Prince MJ, Bird AS, Blizard RA, Mann AH: Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's treatment trial of hypertension in older adults. *BMJ* 312:801–805, 1996

[50]The SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 265:3255–3264, 1991

[51]Forette F, Seux ML, Staessen JA, Thijs L, Birkenhager WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R: Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 352:1347–1351, 1998

[52]Forette F, Seuz M, Staessen JA, Thijs L, Babarskiene M, Babeanu S, Bassini A, Fagard R, Gil-Exremera B, Laks T, Kobalava Z, Sarti C, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Birkenhager WH: The prevention of dementia with antihypertensive treatment. *Arch Intern Med* 162:2046–2052, 2002

[53]Clark CM, Karlawash JHT: Alzheimer's disease: current concepts and emerging diagnostic and therapeutic strategies. *Ann Intern Med* 138:400–410, 2003

[54]Ades PA, Ballor DL, Ashikaga T, Utton JL, Nair KS: Weight training improves walking endurance in healthy elderly persons. *Ann Intern Med* 124:568–572, 1996

[55]Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, Roberts SB, Kehayias JJ, Lipsitz LA, Evans WJ: Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med* 330:1769–1775, 1994

[56]Fine JT, Colditz GA, Coakley EH, Moseley G, Manson JE, Willett WC, Manson JE, Kawachi I: A prospective study of weight change and health-related quality of life in women. *JAMA* 282:2136–2142, 1999

[57]Gregg EW, Williamson DF: Relationship of intentional weight loss to disease incidence and mortality. In *Handbook of Obesity Treatment.* Wadden TA, Stunkard AJ, Eds. New York, Guilford Press, 2002, p. 125–143

[58]Rubenstein LZ, Josephson KR: The epidemiology of falls and syncope. *Clin Geriatr Med* 18:141–158, 2002

[59]Bowen JD, Larson EB: Drug-induced cognitive impairment: defining the problem and finding solutions. *Drugs Aging* 3:349–357, 1993

[60]Gray SL, Lai KV, Larson EB: Drug-induced cognition disorders in the elderly: incidence, prevention and management. *Drug Saf* 21:101–122, 1999

[61]Keister KJ, Creason NS: Medications of elderly institutionalized incontinent females. *J Adv Nurs* 14:980–985, 1989

[62]Hay DP, Rodriguez MM, Franson KL: Treatment of depression in late life. *Clin Geriatr Med* 14:33–46, 1998

[63]Carr-Lopez SM, Phillips SL: The role of medications in geriatric failure to thrive. *Drugs Aging* 9:221–225, 1996

[64]Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM: Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc* 47:850–853, 1999

[65]Talbot F, Nouwen A: A review of the rela-

tionship between depression and diabetes in adults. *Diabetes Care* 23:1556–1562, 2000

[66]Anderson RJ, Freedland KE, Clouse RE, Lustman PJ: The prevalence of comorbid depression in adults with diabetes. *Diabetes Care* 24:1069–1078, 2001

[67]Ciechanowski PS, Katon WJ, Russo JE: Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med* 160:3278–3285, 2000

[68]Newman SC, Hassan AI: Antidepressant use in the elderly population in Canada: results from a national survey. *J Gerontol A Biol Sci Med Sci* 54A:M527–M530, 1999

[69]Dealberto MJ, Seeman T, McAvay GJ, Berkman L: Factors related to current and subsequent psychotropic drug use in an elderly cohort. *J Clin Epidemiol* 50:357–364, 1997

[70]Wilson K, Mottram P, Sivanranthan A, Nightingale A: Antidepressant versus placebo for depressed elderly. *Cochrane Database Syst Rev* 2:CD000561, 2001

[71]Furukawa TA, Streiner DL, Young LT: Antidepressant plus benzodiazepine for major depression. *Cochrane Database Syst Rev* 2:CD001026, 2001

[72]Gill TM, DiPietro L, Krumholz HM: Role of exercise stress testing and safety monitoring for older persons starting an exercise program. *JAMA* 284:342–349, 2000

[73]Williams JW Jr, Mulrow CD, Kroenke K, Dhanda R, Badgett RG, Omori D, Lee S: Case-finding for depression in primary care: a randomized trial. *Am J Med* 106:36–43, 1999

[74]Moore AA, Siu A, Partridge JM, Hays RD, Adams J: A randomized trial of office-based screening for common problems in older persons. *Am J Med* 102:371–378, 1997

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