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“A Veritable Revolution”

5-1 MECHANISMS OF ACUTE CORONARY SYNDROMES AND THEIR INDICATIONS FOR THERAPY: Review Article

Atherosclerotic lesions in humans typically form over the course of years to decades—one of the longest incubation periods among human diseases.

Despite the chronicity of atherosclerosis, thrombotic complications occur suddenly and often without warning.

What mechanisms explain this abrupt transition from stable ischemic heart disease (or asymptomatic disease) to acute coronary syndromes (**ACS**)?

According to the traditional view, progressive stenosis narrows the lumen of an atherosclerotic coronary artery to such an extent that a small platelet thrombus atop the stenosis could occlude the vessel completely. Thus, an occlusive thrombus complicating a high grade stenosis would arrest flow and cause ST-segment elevation myocardial infarction (**MI**).

Our diagnostic tools generally evaluate the ischemia that results from established, fixed stenosis (eg, stress testing and perfusion scanning) or visualizing the stenosis by angiography. Our treatments have targeted the stenosis with the use of percutaneous intervention or bypass surgery.

Pathogenesis of ACS:

Serial angiographic studies have revealed that the plaque at the site of the culprit lesion of a future acute MI often does not cause stenosis that is sufficiently severe to limit flow.

Angiographic monitoring of responses to thrombolytic therapy has shown that, after lysis of the offending thrombus, the underlying stenosis is often not the cause of critical stenosis of the artery.

Computed tomographic angiography, which permits evaluation of the arterial wall (not just the lumen), has shown that the plaques associated with ACS include 1) little or no calcification and 2) outward extension of the arterial wall, a process that tends to accommodate the growth of plaque while minimizing lumen encroachment. Outward expansion of an atherosclerotic coronary artery accommodates the growth of the plaque for much of its history. Luminal stenosis occurs relatively late. Outward expansion of the artery during plaque growth can conceal a considerable burden of atheroma by preventing stenosis—obscuring signs and symptoms of ischemia.

Intravascular ultrasonography has shown that in ACS the culprit lesion often lies proximal to the sites of maximal stenosis—the traditional target of revascularization therapy.

This dissociation between the degree of stenosis and the propensity to provoke an ACS helps to explain why MI often occurs without being heralded by the demand-induced symptoms of angina that would result from a high-grade stenosis.

Clinical data have affirmed that invasive procedures for treatment of stenosis generally do not prevent future thrombotic events.

This assemblage of clinical data challenges the traditional view of the pathogenesis of ACS, which ascribes a leading role to critically stenotic lesions.

Thrombotic Complications of Atherosclerosis:

If the progression of luminal stenosis does not cause many ACS, what does? Most fatal coronary events are due to disruption of a coronary artery plaque. Frank rupture of the plaque's fibrous cap causes the majority of these deaths. Superficial erosion of a coronary artery accounts for the balance of fatal events.

Plaque rupture is the most common cause of fatal ACS. The cap typically overlies the lipid-rich center (the necrotic core) of the plaque, which is filled with trombogenic material. Such plaque often have thin fibrous caps.

A thin fibrous cap has been identified as the best indicator of plaques that cause fatal ruptures. Typically, the sites where plaques rupture have few smooth muscle cells.

Inflammatory Pathways; Thrombosis; Collage Metabolism; and Plaque Rupture and Thrombosis

Inflammation is linked to thinning and weakening of the fibrous cap.

The central lipid core of the plaque forms between the intima and media of the artery. It contains macrophage foam cells and T cells.

The intimal and media contain arterial smooth muscle cells—the source of collagen.

Activated T cells secrete the cytokine interferon, which inhibits production of new collagen required to repair and maintain the plaque's protective cap. T cells also activate macrophages, causing overproduction of interstitial collagenases that breakdown collagen.

Thus, inflammatory signaling puts the collagen in the fibrous cap in double jeopardy—decreasing synthesis and increasing breakdown—rendering the cap susceptible to rupture. These dual actions explain the strong link between inflammation and thrombotic complications of atherosclerosis.

The fibrous cap is important in the pathogenesis of the majority of fatal ACS. The cap owes its strength to the interstitial forms of collagen synthesized primarily by smooth muscle cells. Defects in collagen metabolism contribute to loss of strength of the cap. Since inflammatory cells accumulate at the site of ruptured plaques, and since markers of inflammation predict ACS, it is hypothesized that macrophages (and their mediators) disrupt the collagen in the plaque jeopardizing its strength and precipitating rupture.

Interstitial collagen is usually very stable, but some enzymes (collagenase) are capable of breaking down collagen. These enzymes belong to the matrix-metalloproteinase family (**MMP**). Macrophages, augmented by T-cells, are abundant in plaques and overproduce MMP.

A recent study reported that administration of an inhibitor of MMP in mice yielded an increase in collagen content.

Interventions that increase collagen content of atherosclerotic plaques in animals:

Resection of dietary lipids

Treatment with statins

Introduction of mutations that increase resistance to collagenase.

Treatment with inhibitors of collagenase

Ruptured plaques tend to have large lipid cores, thin fibrous caps, few smooth muscle cells, and abundant inflammatory cells.

Research has focused on the fibrous cap because of its importance in the majority of fatal MI. The cap protects the plaque from rupture. It owes its strength to the interstitial forms of collagen synthesized primarily by arterial smooth muscle cells.

The combined studies of plaque in humans and animals support the concept formulated in theory 1990s. Decreased synthesis and increased breakdown of collagen, controlled by inflammatory signals, leads to a friable fibrous cap and renders the plaque susceptible to rupture. Yet, a weakened fibrous cap alone does not suffice to precipitate plaque rupture, and not all plaques that rupture have thin fibrous caps.

Micro-calcifications within the atherosclerotic intimal can result in a striking increase in circumferential stress and could contribute to rupture.

Superficial Erosion of Plaques:

The mechanisms of superficial erosion are less well understood.

Superficial erosion of coronary atheromata causes about 1/5 of fatal cases of acute MI. It occurs more frequently in women and in patients with hyper-triglyceridemia.

The mechanisms of superficial erosion have received less attention than those involved in rupture of the fibrous cap. Programmed cell death (apoptosis) of endothelial cells could

contribute to their desquamation. Oxidative stress could promote endothelial apoptosis. When cells undergo apoptosis, they produce pro-coagulant tissue factors.

Therapeutic Implications of New Insights:

Although revascularization procedures that target occlusive coronary stenoses relieve anginal symptoms, they have not consistently reduced the risk of ACS or death from CAD. In stark contrast, contemporary medical treatment—notably statins—has prevented both the first and recurrent ACS. Curiously, even though statins reduce events, they have little effect on the degree of stenosis, and result in only modest reductions in atheroma volume. Event reduction that is out of proportion to the shrinkage of stenosis has led to the hypothesis that lipid lowering alters the qualitative characteristics of atheromata, causes modest quantitative improvements in lumen caliber, but may limit the propensity of plaques to rupture. (Ie confers "stabilization"). This distinguishes lipid-lowering interventions from those that address luminal stenosis without altering the molecular and cellular processes that trigger thrombotic complications.

A "lifestyle" intervention in rabbits fed a high fat diet provoked fibro-fatty plaques in the aorta. The rabbits were then switched to a low fat diet. The lipid-lowering diet reduced the content of inflammatory cells, augmented interstitial collagen, and reduced the features that, in human plaques, promote rupture and thrombosis.

In humans, lipid-lowering can increase the fibrous nature of plaques, increasing resistance to rupture. Statins also reduce the lipid content and macrophage activity and promote more fibrous atheromata. Statins have a stabilizing effect on plaques that extends beyond their lipid-lowering action.

Favorable effects of lipid lowering in experimentally produced atherosclerotic plaques:

Reduces inflammation (lowers levels of macrophages, cytokines, and chemokines and expression of leukocyte adhesion molecules

Reduced expression of collagenase (MMP)

Increases interstitial collagen

Lowers levels of oxidized LDL-cholesterol

Reduces production of reactive oxygen species

Increases expression of endothelial nitric oxide synthesis

Reduces thrombotic potential (reduced tissue factor content and activity)

Despite the remarkable benefits of statins, patients appropriately treated with statins are still at considerable risk of ACS. There is need for further interventions. Given the role of inflammation in the pathos-physiological aspects of plaque rupture, studies are assessing anti-inflammatory drugs other than statins to reduce risk. Low-dose colchicine, low-dose methotrexate are being studied as is antibody neutralization of pro-inflammatory cytokines.

Summary

Our understanding of the pathogenesis of ACS has undergone a veritable revolution in the past 20 years.

We understand, in molecular and cellular terms, how most serious thrombotic complications of coronary atherosclerosis occur. Inflammatory pathways have emerged as important drivers of plaque disruption and thrombosis. This expands the scope of treatments.

NEJM May 23, 2013; 368: 2004-1 Review Article by Pete Libby, Brigham and Women's Hospital, Harvard Medical School, Bosom, Mass.
DOI:10.1056/NEJMra1216063

I enjoyed this article. It is long and complex. It took a while to abstract. This is not the final word. Clarifications and additions to the pathogenesis of atherosclerosis will continue.

What has this to do with primary care? A great deal:

Primary care clinicians may not treat the patient when ACS occurs, but they are at the forefront of prevention of atherosclerosis. As the article noted, development of the disease takes years and decades. During this time primary care has the opportunity to prescribe preventive measures.

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"Treat The Patient, Not The HbA1c"

5-2 DIABETES CONTROL IN OLDER PEOPLE: Editorial

Primary care providers must prepare for two important demographic changes—increase in life expectancy, and the fact that we are getting fatter. The prevalence of diabetes is rising across the age spectrum. People over age 65 with diabetes experience higher rates of micro- and macro-vascular complications, leading to increased hospital admissions, higher healthcare costs, and requirement for social care—not the least because of risk of hypoglycemia and associated complications from over-aggressive treatment.

The American Diabetes Association provides new guidelines. Previous guidelines recommended treatment aimed at HbA1c of less than 7% for all adults, regardless of age. New guidelines emphasize the need to tailor treatment for older people. Hypoglycemia, ability to self-management, cognitive status, co-morbidities, and life expectancy are taken into account when making decisions about treatment.

New guidelines offer explicit targets. For patients with little co-morbidity and preserved cognitive and physical function, target is less than 58.5 mmol/mol (7.5%). For those with multiple chronic illnesses and mild cognitive impairment who are at risk for falls and hypoglycemia, the target is less than 64 mmol/mol (8%). In those with end stage chronic illnesses, moderate to severe cognitive impairment, and those in long-term care, target is less than 69 mmol/mol (8.5%)

Recently, a series of high profile studies was unable to show any improvement in cardiovascular outcomes with intensive glycemic control. One study suggested that intensive therapy may result in greater harm to older people.

Older observations suggested an association between hypoglycemia and cognitive and physical decline.

Intensive treatment with the risk of hypoglycemia may outweigh any potential benefit. Tight control can lead to harm.

A target focused on HbA1c is not computable with individualized care because the emphasis is on treating a number rather than the patient.

Recommendations for glycemic control must take into account the increase in the numbers of new drugs available for treatment of diabetes. These drugs may seem to be an attractive option for older people whose glycemic control is suboptimal and who are at risk of hypoglycemia. However, they are expensive, and evidence that they improve patient outcomes on hard endpoints in any age group is lacking.

Iatrogenic risk will be greater in older patients in whom co-morbidity and poly-pharmacy are common.

The benefit of strict glycemic control in the elderly is dubious, and the potential for harm is substantial.

BMJ April 27, 2013; 346:10 Essay, first author Laura A McLaren, Glasgow Royal Infirmary, Glasgow, UK BMJ 2013;346:f2625

JAMA Internal Medicine July 2, 2013; 1731306-07 "Glucose Control In Older Adults With Diabetes Mellitus" First author Kasia J Lipska, Uale University School of Medicine, New Haven, Conn

JAMA Internal Medicine "Association Between Hypoglycemia And Dementia In A Biracial Cohort Of Older Adults With Diabetes Mellitus" First author Kristine Yaffe, University of California, San Francisco

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I enjoyed this essay.

Hypoglycemia places elders at increased risk of acute vascular event; falls, fractures and accident;, and cognitive dysfunction and dementia. It reduces quality of life.

In addition to being at high risk of hypoglycemia, elders are at risk of adverse effects of drugs.

The right choice for a patient at a given point in time requires a careful balance of the circumstances of the patient, his or her goals, and preferences. Shared decision-making promotes patient involvement in treatment decisions to achieve care that is both evidence-based and consistent with the patient's context and values—what matters most to the patient.

But, , one size does not fit all. Elderly patients may not metabolize drugs as rapidly as younger patients. Toxic levels may be reached quickly, even when the "recommended dose" is prescribed. A good rule for many drugs we prescribe for elders is to start at a lower dose, and gradually increase as the clinical picture evolves.

"Treat the patient, not the lab report" should be a general rule for primary care practice, especially for elderly patients. Treating the lab numbers has frequently become a goal in primary care.

We should emulate experienced poker players, who know "when to hold, and when to fold". We should know the patient's goals and preferences and when to shift to comfort-supportive therapy. And try to reduce the numbers of drugs elders take.

I am surprised that the experts shifted from one set of HBA1c targets to another. Reaching HbA1c targets may be onerous even when they are raised to higher levels. It would be better to simply aim to keep frail elderly diabetic patients free of symptoms of uncontrolled diabetes (thirst, excessive urination, unwanted weight loss) and keto-acidosis without considering a number.

The advice to avoid the "newest" drugs is welcome. Primary care clinicians should, in general, wait several years after a new drug comes on the market for clarification of the benefit / harm-cost ratio.

I believe too many drugs are continued much too long in elderly patients. Why continue bisphosphonates, statins, and drugs for cognitive impairment? Some take 8 to 10 different medications daily. This is burdensome. Taking pills becomes intrusive. Daily life can become a ritual of pill-taking. There is absolutely no way anyone can know the adverse interactions of such a mixture of drugs.

Conversion tables (% HbA1c to mmol/mmol) are readily available on the internet. This may be more "scientific", but I see no advantage. It will confuse patients.

Supervised Home Exercise Slows Loss Of Function

5-3 EFFECTS OF THE FINNISH ALZHEIMER DISEASE EXERCISE TRIAL (FINALEX): ***A Randomized, Controlled Trial***

During the past decades, pharmacological research for Alzheimer Disease (**AD**) has been active, but no major breakthrough seems to be on the horizon. Non-pharmacological therapy has promise to improve the quality of life for families of patients with dementia and postpone the need for institutional care.

Intensive, long-term exercise may improve physical functioning in non-institutionalized patients with AD. However, no studies have investigated whether exercise can delay the progress of disability, or how it affects the use and costs of health and social services.

This study investigated the effects of intense and long-term exercise on the physical functioning and mobility of home-dwelling patients with AD.

STUDY

1. Recruited patients (n = 210) who were on the AD register in Finland.

2, Inclusion criteria: Established AD, a spouse living at the same address, age 65 or older, no terminal disease, ability to walk independently. And at least one of the following: At least 1 fall during the past year, decreased walking speed, or unintentional weight loss.

3. Baseline:

Mean age 78. Almost all were receiving AD medication. Divided patients into 3 groups: 1) Home exercise [**HE**], 2) Gym exercise [**GE**]. 3) Control group [**CG**]/ No significant differences between:

CDR Clinical Dementia Rating

FIM Functional Independence Measure

MMSE Mini-mental state examination

SPPB Short Physical Performance Battery

4. The aim was to determine the effect of 2 types of exercise interventions in patients with AD.

5. Patient-caregiver dyads (n = 210) were randomized into 3 groups of 70 dyads: 1) HE group, 2) GE group, and 3) CG group.

HE group performed home-based physical exercise for 1 hour twice a week for 12 months. Physiotherapists, specialized in dementia, administered therapy individually tailored to the patient's needs and problems in daily function and mobility.

GE group performed group-based physical exercise during 4-hour visits to day care centers twice weekly for 12 months under the supervision of physiotherapists. The exercise program consisted of endurance, balance, and strength training. The mean time for individual's training was approximately 1 hour.

CG group (control) received the usual care provided by the Finnish Health Care system. They also received oral and written advice on nutrition and exercise.

6. Participants were assessed at baseline, and at 3, 6, and 12 months.

7. Assessment was based on the caregiver's evaluating of patients' performance at

home.

8. Primary outcome = patients' physical functioning evaluated at each study visit up to 12 months.

RESULTS

1. Results at 12 months:

FIM total score: All groups deteriorated. HE groups deteriorated to a lesser extent

FIM motor score: All deteriorated—HE to a lesser extent

Cognitive scores deteriorated in all groups equally

SPPB deteriorated in all 3 groups equally.

2. Changes in physical functioning during 12 months. (FIM score)

Functioning deteriorated in all 3 groups over time.

Deterioration was significantly slower in the HE group. A significant mean difference between groups appeared at 6 months.

FIM changes at 12 months:

-7.1 HE

-10.3 GE

-14.4 CG

3. Treatment complications and complications:

Adherence to the program was high. The control groups suffered the most falls.

Fracture and hospitalizations did not differ significantly.

4. Complications during the year

	HE (n = 68)	CG (n = 65)
Hospital admissions	29	37
Falls	83	171

Fractures (all)	4	4

5. Total use and costs of health and social services in US dollars were approximately equal in all 3 groups.

DISCUSSION

1. Home-delivered, individually tailored, exercise delayed deterioration of physical functioning without causing any harms.
2. This intervention was administered without increasing costs of total health and social services.
3. There was a 7-point difference in the FIM ratings between the HE group and the CG. The investigators believe that this difference is clinically meaningful because it indicates less need for help in several daily activity categories.
4. There are several reasons why HE intervention was successful in this study: 1) It was tailored to individual patients and performed at home, 2) the exercise was intense and sufficient in duration, 3) the physiotherapists delivering the intervention were specially trained to treat patients with dementia.
5. Adherence among HE patients was exceptionally high, ensuring high levels of training activity.
6. It was surprising that the GE participants did not show significant changes in functioning or mobility scores. However, muscle strength increased remarkably with use of gym training machines. (56% to 81% during the year). Participation was significantly lower than in the HE group. Not all patients with dementia accept group intervention at day care centers.
7. The interventions seemed safe and did not increase falls or fractures. Exercise may reduce falls in patients with AD.
8. It is likely that exercise administered at home will result in better adherence and more favorable effects in respect to functioning.

CONCLUSION

Exercise administered at patients' homes may attenuate the deleterious effects of AD on physical functioning.

This intervention provides new means to help patients with dementia and their families maintain their way of life longer without increasing the total use or costs of health and social services.

JAMA Interan Medicine May 27, 2013; 173: 894-901 Original investigation. First author Kaisu H Pitkala. University of Helsinki, Finland
Doi:10.1001/jamainternmed.2013.359

I believe a similar program could be administered in the USA—likely at higher costs. It would be limited to patients with early dementia. Certainly, not all patients with AD would benefit. And not all family members would participate

Family members could join the patient in exercise at home, and reap the benefits while encouraging the patient. The quality of life of both would improve.

Similar programs could be made available in retirement centers.

Exercise programs could help AD patients maintain some independence, and delay institutionalization and lower risk of falls.

Twelve Weeks Of Mental And Physical Activity Improved Cognition

5-4 THE MENTAL ACTIVITY AND EXERCISE (MAX) TRIAL: ***A Randomized Controlled Trial To Enhance Cognitive Function In Older Age***

Attention is tuning to identification of preclinical disease and development of treatments to prevent or delay onset of dementia. However, there is concern about potential

adverse effects of pharmacological treatment in individuals. Behavioral interventions offer a potential strategy to prevent or delay dementia onset with minimal adverse effects.

There is growing evidence that both physical and mental activity can improve cognitive function in the short term, and may lower risk of developing dementia over the long term. Some previous studies have found that older adults who engage in mental and physical activity are less likely to experience cognitive decline and develop dementia. Several have reported the physical and mental activity may have additive benefits.

To date, randomized, controlled trials (**RCT**) of physical and mental interventions have had mixed results.

This trial compared the effect of different physical and mental activity combinations on cognitive function in community-dwelling older adults with self-reported cognitive complaints.

STUDY

1. Recruited participants by direct mailing, advertisements, and physician and friend referrals. Participants at baseline were age 65 or older with cognitive complaints—positive response to: "Do you feel that your memory or thinking skills have grown worse recently?"
2. No participant was currently engaged in aerobic activity or intensive computer activity. None had dementia (self reported, or based on scoring less than 18 on the modified Telephone Interview for Cognitive Status) or other major neurological or psychiatric disorders.
3. Mental activity groups:

   All participants performed MA independently at home for 60 minutes 3 days per week for 12 weeks.

   MA-I (intervention) group: Performed computer games designed to enhance

the speed and accuracy of visual and auditory processing—games focusing on visual tasks, identifying birds, and identifying targets in peripheral vision. And games focusing on auditory task—distinguishing between similar sounds, following verbal instructions, and answering questions about verbal stories. Program difficulty was adjusted continuously based on each participant's level of performance.

MA-C (active control) group: Watched DVDs for 60 minutes 3 days per week of educational lectures on art, history and science. After each session, participants answered 6 multiple-choice or short answer lecture-specific questions.

4. Exercise groups:

All participants attended group exercise classes.

The EX-I (intervention) class exercised for 60 min 3 days a week for 12 weeks with warm up, 30 minutes of aerobic exercise, cool down, strength training, and stretching and relaxation. Target peak heart rate was 60% to 75% of maximum for participant's age.

The EX-C (control) class had 60 minutes of stretching and toning instead of aerobic exercise. Goal was not to raise heart rate above resting levels.

5. Primary outcome = the 12-week change in cognitive function based on a composite score from a comprehensive neurophysiological battery of 6 tests including measures of verbal learning and memory, verbal fluency, processing speed, executive function, and mental flexibility. Then created a composite cognitive score.

6. Randomized subjects into 4 groups with 31 to 32 individuals in each group:

1) Mental Activity Intervention (MA-I) (Intensive computer + aerobic exercise)

2) Mental Activity Control (MA-C) (Intensive computer + stretching and toning)

3) Exercise Intervention (EX-I) (aerobic + DVD)

4) Exercise Control (EX-C) (stretching + DVD)

7. Compared outcomes in four 2 X 2 groups

MA-I + EX-I ; MA-I + EX-C ; MA-C + EX-I ; MA-C + EX-C

RESULTS

1. Baseline:

Mean age 73; education 16 years; 63% female. Many had history of hypertension, diabetes, myocardial infarction, and were current or former smokers. No significant difference between groups.

On average, participants had moderate to high levels of cognitive function consistent with their age and education level.

No significant differences in baseline cognitive scores between groups.

2. There was significant improvement in composite cognitive scores in all 4 groups. Improvements between the 4 groups varied from 0.08 to 0.21 SD above the mean pre-intervention levels. Overall, the improvement was 0.16 SD.
3. However, there were no significant differences between MA-I and MA-C and between EX-I and EX-.C or when all 4 groups were compared.

DISCUSSION

1. In this RCT, the effects of physical and mental activity interventions on cognitive function in non-demented older adults with cognitive complaints, cognitive scores improved significantly over the course of 12 weeks. But, there were no significant differences between the intervention and control groups.
2. This may suggest that, in this study population, the amount of activity is more important than the type of activity, because all groups participated in both mental activity and exercise for 12 weeks.
3. These findings differ from prior RCTs, which found that similar intensive computer training improved cognitive function more than educational DVDs.
4. There was no difference between the aerobic exercise and stretching and toning groups on global cognitive function. This differs from prior RCTs which found that aerobic exercise increases hippocampal volume compared with strengthening/toning.

5. It is possible that a 12 week intervention is not long enough to achieve a substantially greater aerobic response. It is possible that, in this study population, aerobic and strengthening/toning exercises are equally beneficial.
6. There is growing evidence that less intensive interventions may have cognitive benefits.

CONCLUSION

In inactive older adults with cognitive complaints, 12 weeks of combined mental activity and physical activity was associated with significant improvements in global cognitive function, with no difference between intervention and active control groups.

This may suggest that the amount of activity is more important than the type of activity in this subject population.

JAMA Internal Medicine May 13. 2013; 173: 797-804
doi;10.1001/jamainternmed.2013.189
Original investigation, first author Deborah E Barnes, University of California, San Francisco,

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There has been widespread interest in the possible relation between long-term continued use of mental functions and cognition—likely on the basis of "Use it , or lose it".

I doubt that mental activity and exercise (fitness) will alter the basic patho-physiolgical process of deposition of amyloid in CNS neurons, which is likely a genetic-based process. Mental and physical activity, if prolonged, may improve function of the remaining neurons and pathways (plasticity).

I believe that continued physical exercise will favorably affect cognition—for several reasons. Fitness is related to reduction in risk of hypertension, cardiovascular disease and stroke. As a result, risk of vascular dementia will decrease. In addition, obtaining and

preserving fitness is likely to he a social intervention, which lessens the risk of depression and thus lessens the risk of dementia.

For mental activity, I believe the data are less convincing. It is hard to understand how a 3-month intervention at age 65+ could have lasting effects. I believe it is necessary to continue mental and physical activity throughout old age.

Interventions, if there are any to ward-off dementia, must begin early, before dementia takes hold.

Debate Continues

5-5 VITAMIN D SUFFICIENCY IN PREGNANCY: Editorial

A year ago, the chief medical officers of the UK recommended that all pregnant and breast-feeding women should take a daily supplement containing 400 IU of vitamin D to counter the high prevalence of D deficiency in pregnant women. This was aimed at reducing the associated consequences of deficiency –rickets in childhood and osteomalacia in adults.

A 2011 review found insufficient high-quality evidence to support supplementation. Results for maternal outcomes were inconsistent. In 2012, a Cochrane meta-analysis of 3 trials of daily D during pregnancy found a reduced risk of low birth weight, although not statistically significant.

In a recent combined analysis of 2 RCTs, higher serum D levels at delivery were associated with significantly decreased risk of "co-morbidities" of pregnancy—gestational diabetes, hypertension, infection, bacterial vaginosis, and preterm birth. The study did not have enough power to analyze individual outcomes.

A meta-analysis reported in this issue of BMJ [1] asked: What is the association between maternal levels of serum 25-OH-D and pregnancy and neonatal outcomes? Answer: Vitamin D insufficiency is associated with adverse pregnancy outcomes and birth variables:

	No of studies	Polled odds ratio
Gestational diabetes	10	1.49
Pre-eclampsia	7	1.79
Small for gestational age	6	1.89

Current evidence on D status and neonatal and pregnancy outcomes has derived from observational studies, small trials, low doses of D, unclear processes of randomization and blinding, or low adherence.

The editorialists comment on weaknesses of this meta-analysis: No randomized, controlled trials were included; the largest effect size was derived from case-control studies; poor adjustment for confounding; D deficiency was variously defined and measured at different gestational ages; and other indications of poor quality of the studies included

“Better evidence is required to establish optima levels and need for supplementation”.

Despite these challenges to interpreting the evidence, studies have clear implications. In 2010, the US Institute of Medicine recommended a serum concentration of 25-OH-D of 50 nmol/L should be considered sufficient for bone health. Levels below 50 are common during pregnancy, particularly at high latitudes and in specific populations.

The evidence for a causal association between D deficiency and some maternal and neonatal outcomes is insufficient. But the evidence for bone health is clear cut. The meta-analysis supports D sufficiency in all pregnant women.

Most studies have been done in developed countries. D deficiency is common in Asia and Africa due to the combined influences of dark skin, cultural practices limiting sun exposure, and urban air pollution blocking ultra violet radiation.

BM April 6, 2013; 346: 7 Editorial, first author Robert Lucas, Australian National University, Canberra.

1 “Association between maternal serum 25-hydroxyvitamin-D levels and pregnancy and neonatal outcomes”: Systematic review and meta-analysis. First author Fariba Aghajafari, University of Calgary Alberta, Canada

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There seems to be no end of debates about D supplementation.

If one looks hard enough, some weaknesses can be found in almost all studies.

I believe vitamin D is frequently deficient in the general population of the US, and may be particularly deficient in pregnant women. Food sources of D are limited. Sunlight is the main determinant and is frequently deficient.

I belong to the “Cod liver oil” generation. Many children in the US at that time were given a daily teaspoonful of it to ward off rickets. Not a bad idea.

What should the primacy care clinician do about D particularly in their female patients of child-bearing age? Although they may not attend women during pregnancy, young fertile women are often included in their practice. These women should be protected against D deficiency by supplementation so that they are sufficient should they become pregnant.

Should all younger women have serum levels checked? I believe not. Checking levels for sufficiency is costly, and may lead to burdensome follow-up. I believe it is overdone. It is simpler to empirically prescribe D supplements.

The benefit / harm-cost ratio of D is very high because the denominator of the ration is very small. Harms are nil. Costs are pennies.

Folic acid is the only other vitamin-supplement I can think of that is required in pregnancy—to prevent spina bifida and possibly autism.

Other vitamins and supplements are useless, expensive, and possibly harmful. But they have become part of our culture.