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Richard T. James Jr. M.D.

Editor/Publisher.

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## **7-1 THE EPIDEMIC OF PRE-DIABETES The Medicine and the Politics “Analysis”**

### **Disorders of glucose metabolism:**

#### **1) Diabetes**

**Fasting blood glucose equal to or over 126 mg/dL**

**2-hour post 75 gram glucose load over 200 mg/dL**

**HbA1c 6.5% or higher**

#### **2) Impaired glucose tolerance (IGT)**

**Plasma glucose 2-hour post 75 gram glucose load 140-200 mg/dL**

**(Patients with IGT are at increased risk of developing diabetes and coronary heart disease.)**

#### **3) Impaired fasting glucose (IFG)**

**WHO—plasma glucose 110-125 mg/dL**

**ADA—plasma glucose 100-125 mg/dL**

**WHO—HbA1c 6.0% to 6.4%**

**ADA—5.7% to 6.4%**

#### **4) Pre-diabetes**

**WHO—HbA1c 6.0% to 6.4%**

**ADA 2010—HbA1c 5.7%-6.4%**

**International expert committee 2009: “The categorical clinical states pre-diabetes, IFG, and IGT fail to capture the continuum of risk and will be phased out of use as A1c measurements replace glucose measurements.”**

**The American Diabetes Association (ADA) made changes in diagnosis of pre-diabetes (PD) in the guidelines in 2010. If implemented globally, this would create a potential epidemic, with over half of Chinese adults having PD.**

**PD is an umbrella term to describe a blood concentration of glucose, or HbA1c, that lies above normal but below that defined for diabetes. This includes IGT, IFG, and HbA1c 6.0% to 6.4%.**

**This article explores the evidence and value of PD as a category or diagnosis and argues that the current definition causes unnecessary medicalization and creates an unsustainable burden on the healthcare system.**

**People with impaired glucose tolerance are at increased risk of developing diabetes, with a 10-year incidence as high as 60%. They are also at about 50% greater risk of coronary heart disease.**

Lifestyle interventions can prevent or perhaps delay the onset of diabetes, but the role of other interventions is less clear.

#### **DIAGNOSTIC CHANGE:**

Cut-offs for the diagnosis of diabetes are based on thresholds for risk of retinopathy. Lesser degrees of hyperglycemia increase the risk of developing diabetes and perhaps arterial disease. But the risk is graded, making any choice of cut-off point purely arbitrary.

Between 1979 and 1997, the intermediate category was called “impaired glucose tolerance”. The standard test was measurement of plasma glucose 2 hours after a 75 gram glucose load. The US National Diabetes Data Group defined diabetes as plasma glucose above 200 mg/dL and impaired glucose tolerance (IGT) as 140 to 200 mg/dL. The WHO ratified this definition. But the glucose tolerance test is laborious and inconvenient. It is also poorly reproducible. After recommendations from the ADA and the WHO, the diagnosis of diabetes was altered to fasting plasma glucose 126 and higher, and impaired fasting glucose as 110 to 125 mg/dL.

Recently HbA1c entered as a third test for impaired glucose metabolism. In 2009, there was consensus to use HbA1c 6.5% and higher to diagnose diabetes and levels of 6.0% to 6.4% determined pre-diabetes or impaired fasting glucose. More recently, the ADA lowered the threshold of HbA1c to 5.75% and fasting glucose of 100 mg/dL to define pre-diabetes. This expanded category would roughly double the prevalence of sub-diabetes and include people at lower risk of diabetes and CVD who would perhaps less likely benefit from medical intervention.

#### **EFFECT OF ADA CRITERIA ON PREVALANCE**

A recent study of > 98 000 Chinese adults found a prevalence of impaired glucose tolerance of 8.3%, but over 3 times as many people (27%) satisfied the expanded ADA criteria for impaired fasting glucose and 35% met the criteria for HbA1c. The tests identified a total population of 50% with ADA-defined pre-diabetes. The convenience of HbA1c is likely to influence the diagnostic pattern. Glucose tolerance testing is uncommon, and testing fasting glucose is inconvenient. Measuring HbA1c makes screening simpler, but this will result in the highest prevalence of pre-diabetes.

#### **OVERDIAGNOSIS AND UNDERDIAGNOSIS**

Using the 1) oral glucose tolerance test, 2) fasting glucose and 3) HbA1c to diagnose glucose intolerance is more error prone than for diagnosing diabetes. They have substantial biological and

assay variability. They do not identify the same people. Risk varies with ethnicity and glucose tolerance deteriorates with aging. Impaired glucose tolerance, fasting glucose, and HbA1c reflect different phenomena, and relations with complications such as arterial disease may also differ.

## **QUESTIONS OVER VALUE OF PRE-DIABETES**

The logic of creating a diagnostic category for pre-diabetes is that it can provide benefit by identifying those who may develop diabetes, allowing effective interventions. However, the evidence does not necessarily support this logic. An expert committee of the ADA recommended abandonment of the term pre-diabetes. But the implementation of the new ADA criteria for pre-diabetes is unfeasible. Proving everyone identified by these criteria would place unmanageable demand on health services. “The term pre-diabetes should be put in cold storage.”

**Does diagnosis of pre-diabetes guarantee future diabetes?**

The term pre-diabetes implies inevitable progression and risks stigmatization. A meta-analysis of progression rates of pre-diabetes found that more than half of people identified will be free of diabetes 10 years later.

**Does lifestyle intervention prevent diabetes and its complications?**

Three major trials have examined diabetes prevention by intensive lifestyle counseling. All subjects had impaired glucose tolerance. Each reported a 40% to 60% relative reduction in incidence of diabetes. Follow up study found that lifestyle interventions delayed the onset of diabetes by around 2-4 years, rather than preventing it. The Chinese study of healthy diet and exercise reported a 20-year incidence of severe diabetic retinopathy declined from 16% to 9%, and CVD and all-cause mortality were reduced from 20% to 12% and from 38% to 28% respectively, but only in women. Application of lifestyle interventions like these in millions of people would be challenging.

**What about drugs?**

A RCT of metformin in patients with impaired glucose tolerance over 2.8 years reported a reduced incidence of diabetes by 31%. Long-term follow up showed that metformin delayed diabetes by about 2 years. A trial of rosiglitazone of > 5000 persons with impaired glucose tolerance and a similar trial with pioglitazone followed for 2.4 years reported a reduced incidence of diabetes (relative risk reduction of 62% and 72%).

## **INDIVIDUAL OR POPULATION APPROACH?**

A year before the ADA lowered the HbA1c threshold to 5.7% to define diabetes an international expert committee recommended abandoning the term pre-diabetes and suggested a HbA1c level of 6.0% as the threshold for preventive interventions. The implementation of the new ADA criteria for pre-diabetes is untenable. It will place an unmanageable demand on health services.

The BMJ July 19, 2014 18-20 BMJ2014;349:g4485

“Analysis”, first author John S Yudkin, University College London, London UK

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*I welcomed the opportunity to review the various disorders of glucose metabolism and the likelihood that HbA1c will become the simple standard. This would simplify matters.*

*The authors emphasized that lowering the HbA1c threshold to 5.7% to define PD would place too heavy burden on the public health system. Although primary care clinicians have an abiding interest in public health, their major interest is advising and treating the individual patient. The authors admit that treating pre-diabetes does, at least, delay onset of diabetes and consequently shorten the duration of the disease.*

*Whether one accepts the term “pre-diabetes” or not, there is a state of abnormal glucose metabolism in which the risk of incident diabetes is increased. Treating these patients will delay onset of diabetes in some.*

*The authors stress the population based and socio-economic disadvantages of the concept of “pre-diabetes”, whereas the primary care clinician considers one patient at a time.*

*I believe a defect in glucose metabolism, below that required to diagnose diabetes, is related to increased risk of developing diabetes. Reducing this glucose level will prevent or delay onset of diabetes, and therefore reduce risks of complications of diabetes. If this level exists, it deserves a name. The authors suggest “sub-diabetes”.*

*Patients may have other factors that increase risk of diabetes. These are considered in addition to HbA1c levels: Obesity (especially abdominal obesity) increase body mass index, high BP, abnormal lipids, sedentary lifestyle, and family history of diabetes. These factors increase the likelihood of “pre-diabetes”. Correcting them will prevent or delay diabetes, whether or not the word “pre-diabetes” is abandoned or not.*

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## **7-2 NON-CARDIOVASCULAR EFFECTS ASSOCIATED WITH STATINS: State of the Art Review**

**Statins are taken by more than 200 million people worldwide.**

**In randomized controlled trials (RCTs) and meta-analyses of primary and secondary prevention trials, statins have produced a significant reduction in incident myocardial infarction, stroke, and death from CVD in all patients and all-cause mortality in high-risk patients. As well as lowering LDL-cholesterol, statins are thought to have anti-inflammatory and direct effects on plaque, leading to plaque stabilization, and even modest regression of atheromas.**

**Most recent US guideline for statin use in adults over age 21.**

- 1. Clinical ASCVD**
- 2. LDL-c over 190**
- 3. Diabetes (type 1 or 2) in patients age 40-75**
- 4. Estimated 10-year ASCVD risk 7.5% — age 40-75**

**When used in primary prevention, statins are generally prescribed to asymptomatic people for prolonged periods. Risks must be carefully weighed against benefits. Although statins are well tolerated by most people, there are widespread concerns about potential harms.**

**This review aims to provide a balanced evaluation of the available evidence on the potential non-cardiac harms associated with use of statins.**

### **MYOPATHY**

**Myopathy associated with statins occurs in several different forms. The definitions vary across studies.**

**1) Rhabdomyolysis is the most severe form. It is often defined as a creatine kinase (CK) at least 40 times greater than normal or increased CK associated with renal failure. Rhabdomyolysis is estimated to occur in 1 per 10 000 person-years. Risk of rhabdomyolysis is much higher in patients taking high-dose statins (eg, simvastatin 80 mg vs 20 mg). There may be increased risk of rhabdomyolysis when other drugs (eg, fibrates) are taken with statins. Studies of cerivastatin reported a 12-fold increase risk of rhabdomyolysis compared with placebo. Cerivastatin was withdrawn from the market.**

**2) Myositis is defined as muscle pain in association with a CK concentration greater than 10 times normal. In a meta-analysis of RCTs of more than 17 000 patients, overall incidence of myositis was estimated at 1 per 2000 person-years**

3) Myalgia is muscle pain without increased CK. It was reported in 21 studies of over 48 000 patients. The relative risk of myalgia in statin patients vs placebo was 0.90. Only atorvastatin (*Lipitor*) was associated with increase in myalgia when compared with placebo. In a more recent analysis (over 46 000 primary preventions patients) there was no significant difference between statins and placebo (7.9% vs 7.6%)

The meta-analyses of RCTs suggest that statins are associated with modest increases in myositis and rhabdomyolysis, but not with myalgia. The risk is largely confined to treatment with high-dose statins, particularly high-dose simvastatin (80 mg), which is no longer recommended.

Concerns and criticisms: Despite the generally reassuring data from RCTs, there remains widespread concern regarding statin myopathy. Much of the concern arises from uncontrolled observational studies, where the incidence of statin-associated myalgia is reported, than in RCTs. In an observational study of over 35 000 adults, the prevalence of any musculo-skeletal pain in the previous 30 days in statin users vs non-users was 22% vs 17%. In another study of over 7900 consecutive patients using statins, 10% of patients reported muscle-skeletal pain. Randomized trials have also reported similarly high incidence of muscle skeletal pain, but with no difference between statins and other groups.

Genetic susceptibility to myopathy: More recently there has been concern about the effect of statins on muscle strength and function. Recent research has focused on identification of patients with increased genetic susceptibility to statin myopathy. One small study of patients with definite statin myopathy reported a single nucleotide polymorphism that was strongly associated with statin induced myopathy.

Re-challenge: Recent observational data show that most patients who develop muscle symptoms while taking statins can be safely restarted on a statin. In a cohort of 1600 patients referred for statin intolerance, 73% were able to tolerate a less intensive dosage. In an observational cohort of over 6500 patients whose statin was discontinued because of side effects, 92% could tolerate a statin when re-challenged.

## DIABETES

Randomized trials have shown a consistent increase in incident diabetes associated with statins. The mechanism is not known. In one large study, over a mean of 2 years, incident diabetes was higher with rosuvastatin (*Crestor*) than with placebo. Incident diabetes is influenced by the dose and potency of the statin. The increased risk seems to be confined mainly to people who are already at high risk for diabetes and in people with 2 or more components of the metabolic



syndrome. It is not known whether the increased risk of diabetes is mitigated by the benefits of statins. It is also unknown whether cessation of statins reverses the diabetes.

## **LIVER**

In a meta-analysis of over 75 00 patients treated with various statins, the incidence of liver transaminase levels greater than 3 times normal was 1.14% vs 1.05% of those taking placebo. High dose statins was associated with a 4-fold greater risk than low dose. No case of liver failure occurred. The US guidelines recommend baseline transaminase levels be measured before starting a statin.

## **DEMENTIA AND COGNITION**

In 2012, the FDA added a warning to statins that some patients may experience “ill-defined memory loss” and “confusion”. This was based on a small number of randomized trials and observational data. The fear of cognitive decline has been popularized in the media. Conversely, statins may have beneficial effects on cognition by reducing risk of vascular dementia. In a trial of over 5500 adults age 70-82, of pravastatin vs placebo with a follow-up of 3.5 years, cognition declined in both groups, with no difference between groups. Eight studies of long term cognition found no association; 5 showed a benefit from statins. A recent systemic review reported a 21% decrease in Alzheimer’s disease in statin users vs non-users.

## **KIDNEY**

### **Contrast-induced nephropathy:**

Acute kidney injury is a common adverse event in patients exposed to iodinated contrast material. Recent RCTs have shown that even a single high dose of a statin (atorvastatin) reduces the incidence—4.5% vs 18%. Pre-treatment with a statin prior to administration of a contrast material likely reduces incidence of contrast nephropathy.

## **PANCREATITIS**

A reduction in the cholesterol content of bile, with a decreased risk of gallstones is proposed as a potential mechanism for the effect of statins on the risk of pancreatitis. In controlled trials of over 11 000 patients followed for 4 years, 134 people taking statins developed pancreatitis vs 175 taking placebo (relative risk = 0.77).

## **RANDOMIZED VS OBSERVATIONAL EVIDENCE**

**Mammy patients experience the onset of symptoms in temporal association with starting a statin. This often leads to suggestions that the statin is responsible for a variety of side effects, including myalgia and memory loss, even when there are few or no RCTs to support these claims. The evaluation of subjective side effects using observational data is inherently biased. In a “N of 1” study of patients who experienced myalgia while being treated with statins, patients were randomly assigned to placebo or to be re-challenged with the same statin. There was no difference between statin and placebo in myalgia score. Some patients resumed statin therapy.**

## **BALANCE OF BENEFITS AND HARMS**

**Recent US cholesterol guidelines may increase the number of adults eligible for statin treatment by as many as 13 million. RCTs and meta-analyses show significant and consistent reductions in CVD events and all cause mortality in nearly all populations averaging a 21% relative reduction in risk per 1.0 mmol/L reduction in LDL-cholesterol regardless of baseline LDL-c and CVD risk. The benefits of statins far outweigh the harms.**

## **CONCLUSION**

**Statins cause a modest increase in incidence of severe myopathy, but are not associated with a significantly increased risk of myalgia. Muscle toxicity occurs in the setting of very high dose statins or in the presence of drugs that interact with statins, eg, gemfibrozil. Statins increase the risk of incident diabetes although the risk is largely confined to patients who have preexisting risk factors for diabetes. Statins reduce the incidence of contrast-induced nephropathy and pancreatitis.**

**Further research is needed to elucidate the association between statins and cognition, erectile dysfunction, COPD, and cataracts.**

**The BNJ July 26, 2014; 3-38 BMJ2014;369:g3942**

**State of the Art Review, first author Clinton S Desai, Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore MD**

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*The article also discussed cataracts, venous thromboembolism, acute kidney injury, erectile dysfunction, COPD, cancer, and fatigue, all of which have been suggested to be adverse effects of statins. The data in the literature is not sufficient to suggest any association.*

*Since many primary care clinicians have patients taking statins, I welcomed this overview. Patients with myalgia, after full explanation of harms and benefits, may express their desire to continue or discontinue the statin according to their personal preference. Determination of CK levels will be a big help.*

*This gave me an opportunity to review components of the metabolic syndrome*

- 1. Abdominal obesity*
- 2. Increased triglycerides*
- 3. Decreased HDL-cholesterol*
- 4. Hypertension*
- 5. Elevated fasting blood glucose (Insulin resistance)*

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### **7-3 SHOULD COLORECTAL CANCER SCREENING BE CONSIDERED IN ELDERLY PERSONS WITHOUT PREVIOUS SCREENING? Analysis**

The US Preventive Services Task Force (USPSTF) recommends colo-rectal cancer (CRC) screening using fecal occult blood testing, sigmoidoscopy, or colonoscopy, starting at age 50 and continuing until age 75. USPSTF recommends against routine screening persons over age 75 who have a history of adequate screening, but does not address screening elderly patients who have not undergone previous screening. These recommendations have led many members of the medical community to believe that no one over age 75 should be screened.

However, because unscreened elderly persons are at greater risk for CRC than adequately screened persons, screening is likely to be effective, and cost-effective up to a more advanced age. If so, the lack of more specific recommendations on the age to stop screening may result in an unfounded denial of access to screening in elderly people who were never screened for CRC—a group representing 23% of the US persons older than 75.

Many elderly people continue to be screened up to their late 80s or early 90s. However, at these ages, continued screening is not likely to be cost-effective, even in those without previous screening. This is because the high risk for death of competing disease at advanced age tends to offset the benefits of screening and because the risks of harms due to screening (colonoscopy-related complications, and over-diagnosis and overtreatment of CRC) increase with increasing age.

The object of this study was to determine up to what age CRC screening should be considered in elderly persons without previous screening, and to determine which screening test—colonoscopy, sigmoidoscopy, or fecal immune-chemical testing (FIT)—is indicated at what ages. The study also performed separate analyses for elderly persons with no, moderate, or severe comorbid conditions because effectiveness and cost-effectiveness of screening depends on a person's life expectancy.

## **METHODS**

Used the Micro-Simulation Screening Analysis-Colon model (Erasmus University Medical Centre, Rotterdam, Netherlands) to quantify the effectiveness and costs of screening. It is a well-established micro-simulation model for CRC developed at the University. It contains underlying assumptions and calibrations which simulate the life histories of a large population from birth to death. As each simulated person ages, 1 or more adenomas may develop and progress into CRC. Survival after clinical detection is determined by the stage at diagnosis, the localization of the cancer, and the person's age.

*(I did not pursue this application further because of lack of time. It will rarely be used hereafter in Practical Pointers. As stated, it depends on some assumptions. The model is available in the appendix of Annals ([www.annals.org](http://www.annals.org)) Ed.)*

For each age between 76 and 90, the study simulated a cohort of 10 million elderly persons without previous screening with no, moderate and severe comorbid conditions. Compared with adequately screened elderly persons, the risk of CRC is substantially greater. Of simulated patients age 80 with negative screening at ages 50, 60, and 70, at age 80 CRC was present in 0.3% and adenomas in 14.1%. In simulated patients age 80 without previous screening, CRC was present in 2.6% and adenomas in 44.9%.

Persons were classified as having moderate co-morbid conditions if they had any ulcer, rheumatologic disease, peripheral vascular disease, diabetes, paralysis, cerebro-vascular disease, or a history of acute myocardial infarction; severe comorbid conditions if they had COPD, congestive heart failure, moderate or severe liver disease, chronic renal failure, cirrhosis, dementia, chronic hepatitis, or AIDS; and no comorbid conditions if none of these conditions was present.

Screening prevents cancer by leading to removal of adenomas, thereby reducing years living with CRC and improving quality of life. Conversely, screening results in over-diagnosis and overtreatment of cancer in persons who otherwise would never have been diagnosed or bothered with cancer if they had not been screened, and hence a loss of quality of life.

Cost-effectiveness was based on the assumption that there is a willingness to pay \$100 000 per year of quality adjusted life.

## **RESULTS**

**Effectiveness:** The effectiveness of CRC screening in unscreened elderly persons declines with age. A 1-time colonoscopy in healthy persons age 90 prevented 4.5 CRC deaths per 1000 vs 11.9

per 1000 in healthy persons age 76. In healthy 90-year old persons, colonoscopy resulted in over-diagnosis and overtreatment of 7.7 CRC cases per 1000. This resulted in a net harm (1.7 QALY were lost per 1000). One-time sigmoidoscopy and especially 1-time FIT were generally less effective than 1-time colonoscopy.

**Costs:** The net costs of screening increased substantially with age. Colonoscopy was the most expensive. The assignment of LYs lost with CRC works two ways: 1) Detection and removal of adenomas reduces LY lived with cancer resulting in a gain in length and quality of life. 2) Screening results in over diagnosis and overtreatment, resulting in LYs lived with cancer care in persons who would never have been diagnosed or bothered with cancer without screening.

## DISCUSSION

In elderly persons who have never been screened for CRC, screening is cost-effective well beyond age 75.

One-time screening strategy indicated by age:

| Co-morbid condition level | Age up to which CRC screening should be considered | Screening Strategy indicated, by age |               |       |
|---------------------------|--|--------------------------------------|---------------|-------|
|                           |  | Colonoscopy                          | Sigmoidoscopy | FIT   |
| None                      | 86   | 76 to 83                             | 84            | 85-86 |
| Moderate                  | 83   | 76 to 80                             | 81            | 82-83 |
| Severe                    | 80   | 76 to 77                             | 78            | 79-80 |

Although the incidence of CRC increases up to very advanced ages, the effectiveness and cost-effectiveness of screening decline with increasing age. This is primarily due to increasing risks for other-cause death. The risks for screening-induced harms (colonoscopy-related complications and over-diagnosis and over-treatment) also increase with age.

Colonoscopy every 10 years, sigmoidoscopy every 5 years, and FIT every year are almost equally effective when applied from ages 50 to 75. But because colonoscopy is more costly, and the effectiveness of all screening tests is marginal at very advanced ages, screening with colonoscopy is not cost effective compared with sigmoidoscopy and FIT at the most advanced ages.

Screening with colonoscopy as recommended by the USPSTF (at ages 50, 60, and 70) requires 30 to 35 colonoscopies per life year gained.

Screening with colonoscopy in unscreened persons age 83 with no co-morbid conditions, requires 32 colonoscopies per life year gained.

## CONCLUSION

In the 23% of elderly persons in the US who haven't ever been screened for CRC, screening should be considered well beyond age 75.

Screening with colonoscopy is indicated at most ages.

Annals Internal Medicine June 20, 2014; 160: 750-759 "Analysis", first author Frank van Hees, Erasmus University, Rotterdam, Netherlands.

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*I find modeling studies difficult to abstract.*

*This analysis lumps subjects into large groups (e.g., all persons age 80; all with congestive heart failure; all with a history of myocardial infarction). But, all individual persons in the categories of moderate and severe co-morbidities differ, and, in practice, must be considered individually.*

*I do not understand why they include persons with dementia, congestive heart failure, and renal failure as candidates for colonoscopy. They do not mention that the pros and cons of screening must be discussed with individual patients for consideration.*

*The study makes broad assumptions. Not all (indeed few) would set the value of a quality-year-of-life at \$100 000.*

*The authors do not stress adverse complications of colonoscopy (perforation, hemorrhage), which would be a calamity in a healthy elderly patient undergoing a screening procedure. I believe screening with FIT would be more acceptable for many elderly persons who had never been screened before.*

*Nevertheless, the model does point out that screening is an important clinical intervention in many elders who have never been screened before. The prevalence of adenomas and CRCs in these patients is high. Screening will lead to lengthening the healthy life-years of some patients. Primary care clinicians should discuss the possible advantages in very select elderly patients.*

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## 7-4 EXERCISE FOR DEPRESSION JAMA Clinical Evidence Symposium

Depression is commonly treated with medications or psychological therapies. Some consider exercise as an adjunct or substitute treatment.

This symposium summarizes and updates a Cochrane Review that assesses whether exercise is associated with improvements in depression.

## **Summary of findings:**

**Thirty seven trials provided data for meta-analysis; 35 trials compared exercise with no treatment or a “control intervention”.**

**Because different depression scales were used, standardized mean differences (SMD) were used to combine data. A SMD of 0.20 represents a small effect; 0.50 a moderate effect; and 0.80 a large effect.**

**The authors converted SMD to the Beck Depression Inventory (BDI) score. The BDI, a self-rating depression scale includes 21 items, each scored as 0 to 3, giving a maximum score of 63. Scores below 10 are considered minimal depression; scores above 30 indicate severe depression.**

**Exercise was associated with a greater reduction in depression scores compared with controls (35 trials; pooled SMA -0.62.) . This represents a difference of approximately 5 BDI points.**

**The article presents 16 trials of the effect of exercise vs control or placebo on the BDI. All but 3 favored exercise. The overall benefit was reduction of 4.76 points on the BDI. Most trials were small, many had methodological weakness. Recruitment was often not representative of the population at large.**

**However, analyzing only the 6 trials with adequate allocation concealment, intention-to-treat analysis, and blinded outcome assessment (n = 464) showed no association of exercise with improved depression.**

**Seven trials (n = 189) showed no difference between exercise and psychological therapy. Four trials (n = 298) found no difference between exercise and antidepressant drug therapy.**

**The SMD for aerobic exercise indicated a moderate clinical association (SMA -0.55). The SMD for resistance exercise (-1.03; BDI -9.79) indicated a stronger association.**

**There was also a moderate favorable association between exercise and reduction in depression scores in studies that reached a clinical diagnosis of depression by interview (BDI -5.4)**

**Studies with long-term follow-up (8 trials; n = 377; duration of follow-up 4 to 26 months) reported only a small favorable association (BDI -3.14)**

**No trial reported an increase in adverse events associated with exercise.**

## **Discussion:**

**Exercise may have a moderate-sized favorable association with depression. But because of risk of bias, this association may be small.**

**The optimal type, intensity, frequency, and duration of exercise on depression remain unclear.**

Adherence to exercise may be determined by the severity of the depression, but there was insufficient evidence to assess this.

The UK National Institute for Health and Clinical Excellence (NICE) recommends structured exercise, 3 times a week, for mild to moderate depression.

**Bottom line:** Exercise was associated with a greater reduction in depression symptoms compared with no treatment, placebo, or active control interventions such as relaxation or medication. However, the benefit was small.

JAMA June 18, 2014; 311: 2432-33 “JAMA Clinical Evidence Synopsis”, first author Gary Cooney, Royal Edinburg Hospital, UK

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*Not a conclusive study. More, long-term observation is required.*

*Anecdotally, I had a patient—a middle-aged man who became moderately depressed after the death of his wife. He began walking in his neighborhood every day. He walked, and walked and walked some more. Walking relieved his symptoms of depression.*

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#### 7-5 VITAMIN D AND MORTALITY: Meta-analysis of Individual Participant Data from a Large Consortium of Cohort Studies from Europe and the United States

Mean serum 25(OH)D (D) concentrations vary by country, sex, and season. It is not clear how much these variations affect the prognostic associations of low D concentrations with mortality.

This study found that lowest D levels were consistently associated with increased incidence of all-cause and cause-specific mortality, although the association with cancer mortality was only in patients without a history of cancer.

In clinical practice, cut-off values for D deficiency might need to be made region-, sex-, and season-specific in order to identify those in populations with relatively low D concentrations.

#### Participants and setting:

Meta-analysis included 26 018 men and women age 50-79 from eight cohorts in Europe and the US with follow-up between 4.2 and 15.9 years.

| Population       | Outcome             | Risk ratio |
|------------------|---------------------|------------|
| Total population | All-cause mortality | 1.57       |



|  |                  |      |
|--|------------------|------|
| Subjects without history of cardiovascular disease | CVD mortality    | 1.65 |
| Subjects with a history of CVD                     | CVD mortality    | 1.47 |
| Subjects with a history of cancer                  | Cancer mortality | 1.70 |
| Subjects without a history of cancer               | Cancer mortality | 1.02 |

Effect estimates in the three other D fifths (compared with the fifth with the highest D levels) were weak or absent.

These results were constant across cohorts, sex, age, and seasons of blood drawn even though the cut-off values set at the fifths varied by cohort and by age, sex, and season.

The main limitation of this study is its observational nature. Despite adjustment for known potential confounders, the possibility remains that the observed associations are confounded by other unmeasured factors.

Conclusion: Despite strongly varying 25(OH)D levels by country, sex, and season of blood drawn, the association between the D levels and all-cause and cause-specific mortality was remarkably constant.

The BMJ June 20, 2014;348:13 Meta-analysis, first author Ben Schottker, German Cancer Research Center Heidelberg Germany

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*A provocative, but not a strong study. I am not convinced. No mention of a possible mechanism for the results.*

