

PRACTICAL POINTERS
FOR
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MEDITERRANEAN DIET [2-1]**

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A Substantial Reduction In The Risk Of Major CVD Events Among High-Risk Persons.

[2-1] PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE WITH A MEDITERRANEAN DIET: A Randomized Trial

The traditional Mediterranean Diet (**MD**) is characterized by:

High intake of olive oil, fruit, vegetables, and cereals;

Moderate intake of fish and poultry;

Low intake of dairy products, red meat, processed meats, sweets:

Wine in moderation, consumed with meals.

Increasing adherence to the MD had been consistently beneficial in reducing cardiovascular risk.

This randomized trial tested the efficacy of two experimental MDs¹ as compared with a control diet (low fat) on primary prevention of cardiovascular disease (**CVD**).

STUDY

1. A parallel-group, multicenter, randomized trial entered 7447 participants, mean age 67. None had known CVD at enrollment. All had either type-2 diabetes, or at least 3 major risk factors: smoking, hypertension, elevated LDL-cholesterol, low HDL-cholesterol, overweight or obesity, family history of premature coronary heart disease. (High risk group)
2. Beginning in 2003, participants were randomly assigned, in a 1:1:1 ratio to: 1) MD + extra-virgin olive oil,²) MD + nuts, and 3) low fat diet (control).
3. Participants received periodic training sessions from a dietician,. General medical, and food frequency and leisure-time physical activity questionnaires were administered yearly.
4. Biomarkers periodically checked compliance: 1) urinary hydroxytyrosol levels for olive oil, and 2) plasma alpha-linolenic acid for nuts.
5. Primary endpoint = composite of: myocardial infarction, stroke, and death from cardiovascular causes.
6. Duration of study 2003-2010. The stopping boundary for statistically significant benefit of the MDs with respect to the primary endpoint was crossed at the interim evaluation. The data and safety monitoring board recommended stopping the trial as of December 1, 2010.

RESULTS

1. Baseline characteristics

Baseline	MD + EVOO	MD + nuts	Control
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	n = 2543)	n = 2454)	n = 2450)
Female %	59	54	60
Age (mean)	67	67	67

Almost all were white, from Europe. Multiple other possible risk factors were similar between groups.

2. Followed participants for a median of 4.8 years. Over time 523 were lost to follow-up.
3. Compliance: Participants in the 2 MD groups significantly increased weekly servings of fish, legumes, EVOO, and nuts. There were no changes in physical activity during the trial.
4. Outcomes:

A. Primary endpoint:	MD + EVOO	MD + nuts	Control
Person-years	11 852	10 365	9763
Number of events	96	83	109
Rate per 1000 person-years	8.1	8.0	11.2
Hazard ratio (HR) vs control	0.70	0.72	1.00 (referent)
B. Secondary end-points			
Stroke			
Number of events	49	32	58
Per 1000 person-y	4.1	3.1	5.9
HR vs control	0.67	0.54	1.00
Myocardial Infarction (MI)			
Number of events	37	31	38
Per 1000 person-y	3.1	3.0	3.9
HR vs control	0.80	0.74	1.00
Death from CVD			
Number	26	31	30
Per 1000 person-y	2.2	3.0	3.1
HR vs control	0.69	1.01	1.00

(Regarding components of the primary end-point, only the comparison of stroke risk reached statistical significance.)

DISCUSSION

1. Energy-unrestricted MD, supplemented with either EVOO or nuts, resulted in an absolute risk reduction of approximately 3 major cardiovascular events per 1000 person-years (a reduction of approximately 30%) among high-risk persons who were initially free of CVD. These results support the benefits of the MD for CVD risk reduction.
2. This is particularly relevant given the challenges of achieving and maintaining weight loss.
3. The risk of stroke was reduced significantly in the 2 MD groups. The risk reduction of MI and CVD mortality did not reach statistical significance.
4. These results compare with the Women's Health Initiative Dietary Modification Trial, in which a low-fat diet resulted in no CVD benefit.
5. The generalizability of the findings is limited because all study participants lived in a Mediterranean country and were at high CVD risk.
6. The major between-group differences involved the supplements: EVOO and nuts. The supplements were probably responsible for most of the observed benefits.
7. The small between-groups differences in the diets during the trial are probably due to the fact that, for most participants, the baseline diets were similar to the MD, and the control group was given recommendations for a healthy diet.

CONCLUSION

In this primary prevention trial, energy un-restricted MD supplemented with EVOO or nuts, resulted in a substantial reduction in the risk of major CVD events among high-risk persons.

The results support the benefits of the MD for primary prevention of CVD.

NEJM February 25, 2013 at NEJM.org. DOI:10.1056/NEJMoa1200303

Prevençion con Dieta Mediterranea: The PREDIMED trial, first author Ramon Estruch, Department of Internal Medicine, Hospital Clinic, Barcelona, Spain

Funded by the Spanish government Instituto de Salud Carlos III

The print article appeared in NEJM April 4, 2013 DOI:10.1056/NEJMoa1200303

Not a strong study. The diet did not represent the cultural MD because of the addition of nuts and EVOO.

Generalizability is limited because the study was conducted in a country in which the MD is common. Subjects at baseline were past middle age. The study was of short duration. Longer duration

and more participants would add greater statistical significance if the MD were to be continued throughout life, I believe results would be more definitive.

1 RESEARCH “MEDITERRANEAN DIET”

	≥
Fresh fruits	3 servings / d
Vegetables	2 servings / d
Fish; seafood	3 servings / wk
Legumes	3 servings/ wk
Sfrito ³	2 servings/ wk

White meat Instead of red meat

Wine⁴ 7 glasses / wk

Supplements in the trial

 EVOO¹ 4 tbsp / d

 Nuts² 3 servings / wk (30 g each)

1 Includes use for cooking and salads. In the trial, the goal for those assigned was to consume 50 g or more per day.

2 Mixed almonds, walnuts and hazelnuts

3 A sauce made with tomatoes and onions, and often garlic and aromatic herbs. Slowly simmered with olive oil

4 Wine is optimal, only for habitual drinkers.

Discouraged

Soda drinks

Commercial bakery goods

Spread fats

Red meat

Processed meat

2 EXTRA VIRGIN OLIVE OIL (EVOO)

According to the International Olive Oil Counsel, EVOO is obtained only from the olive (unadulterated). Olives are harvested under conditions (particularly thermal conditions) which do not

alter the oil in any way. It has not undergone any treatment other than washing, decanting, centrifuging, and filtering. This excludes oil obtained by use of solvents or re-esterification methods, and those mixed with oils from other sources.

It has a fruity acidity, from oleic acid of no more than 0.8 grams per 100 grams, and other characteristics fixed by the IOOC. The oil accounts for less than 10% of oil produced. It is the highest quality olive oil.

The US has not adopted this definition as a legal standard. This allows lower quality oils to be legally labeled as EVOO. Source: The Olive Oil Source.

Higher Fitness Levels In Midlife Were Associated With A Lower Risk Of Dementia

[2-2] THE ASSOCIATION BETWEEN MIDLIFE CARDIO-RESPIRATORY FITNESS LEVELS AND LATER-LIFE DEMENTIA: *Prospective Observational Primary Prevention Study*

One in 8 persons age 65 and older has Alzheimer disease (AD). Costs for their care rise to over \$200 billion annually, and will increase.

Identifying preventable causes of dementia is critical. The most cost-effective measures to prevent AD would be mediated through life-style changes, which require minimal medical intervention.

This study evaluated the association between objectively measured midlife fitness levels and later development of dementia. Previous analyses have shown that high fitness levels protect against all-cause mortality, stroke, and diabetes.

STUDY

1. Participants (n = 19 458; mean age 50) were community-dwelling, generally healthy persons who received extensive preventive health examinations including a maximal treadmill exercise test at baseline (in midlife).
2. Fitness level was measured as maximal time on the treadmill, which is highly correlated with maximum oxygen uptake (VO₂max).
3. All were later matched with their Medicare data for claims for dementia.
Most had their baseline examination more than 9 years before Medicare entry.
4. Divided participants into sex- and age-specific quintiles of fitness levels. Quintile 1 was considered “low fit”, which historically was most highly associated with increased morbidity and mortality. Quintile 5 was considered most fit.
5. Primary outcome = all-cause dementia defined as having at least 3 years of

Medicare coverage with a diagnosis of dementia (including AD, vascular dementia, senile and presenile dementia).

6. Determines the overall prevalence of all-cause dementia at attained ages, 70, 75, 80, and 85.

RESULTS

1. Median follow-up from the baseline examination was 25 years; a mean of 7 years of observation of the Medicare data. A total of 1659 cases of incident all-cause dementia occurred during 125 000 total person-years.
2. Lower fitness levels at midlife were associated with higher prevalence of traditional cardiovascular risk factors, increased BMI, hypertension, diabetes, hyperlipidemia, and smoking.
3. Prevalence of dementia: 0.8% at age 70; 2.9% at 75; 8.3% at 80; and 14.8% at 85.
4. Higher fitness levels in midlife were associated with a lower risk of dementia (HR quintile 5 vs quintile 1 = 0.64). (Adjusted HR: Q1 = 1.00 (referent); Q2 = 0.88; Q3 = 0.79; Q4 = 0.70; Q5 = 0.64)
5. There was no difference between those with higher education levels vs those with lower levels. There was no difference between those with and without previous stroke, suggesting that the association between higher fitness and risk of dementia is independent of intervening cerebrovascular disease.

DISCUSSION

1. In this cohort of generally healthy community dwelling persons having previous health examinations, there was association between higher midlife fitness levels and lower risk for dementia in later life, independent of cardiovascular risk factors. The study specifically addressed measured fitness levels rather than self-reported behaviors.
2. The association was independent of hypertension, diabetes, smoking, BMI, and serum lipids.
3. A recent NIH consensus statement suggested that physical activity (PA) prevents dementia. A large 5-year Canadian study of 4615 participants showed that PA vs no PA, was associated with a lower risk of cognitive impairment and AD. Some studies report conflicting outcomes.
4. What might be the mechanism? Enhanced fitness is associated with lower risk of

diabetes and hypertension, which are established risk factors for dementia. Fitness may be related to greater blood flow in the brain.

5. Fitness levels are modifiable through training. Previous reports have shown that exercise of at least moderate intensity for at least 150 minutes per week over 5 to 6 months results in improvement of 1 to 2 METs in fitness levels. PA in midlife may lead to improved fitness levels, resulting in less all-cause dementia with aging.

CONCLUSION

Higher midlife fitness levels were associated with lower hazards of developing all-cause dementia in men and women older than age 65.

Annals Internal Medicine February 5, 2013; 158: 162-68 Original investigation, first author Laura R DeFima. The Cooper Institute, Dallas, TX.

The Cooper Center Institute Longitudinal Study (CCLS)

Supported in part by the National Heart, Lung, and Blood Institute and the American Heart Association.

The study measured outcomes in participants (fit, but less fit) vs the very high-fit. Those classified as low fitness were likely more fit than the average middle-aged American.

Can these results be applied to those who are unfit vs those that are above average fitness? Can the results be applied to the general population? I believe they can.

Will these results motivate the general population? I doubt it. However we must continue to be advocates of PA throughout the lifespan by setting examples and by repeatedly reminding patients of its importance.

Practical Pointers has abstracted many articles dealing with the health advantages of lifestyle interventions: Diet; weight control; exercise and fitness; smoking; alcohol. Primary care clinicians should be at the forefront in encouraging healthy lifestyles. Patients should be asked repeatedly to review these factors, regardless of the reason for the consultation. Giving a healthy-living check list might help.

The brief list could simply state: Exercise, weight control, diet, smoking, and alcohol.

Primary care clinicians should be chief advocates of healthy living.

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Both Statins And Increased Fitness Lowered Mortality Significantly And Independently

[2-3] INTERACTIVE EFFECTS OF FITNESS AND STATIN TREATMENT ON MORTALITY RISK IN VETERANS WITH DYSLIPIDEMIA: A Primary Prevention, Cohort Study

Statin treatment substantially reduces morbidity and mortality in individuals with established coronary heart disease (**CHD**). Statins also provide health benefits for individuals at high risk for CHD.

Lifestyle changes are also important in reducing cardiovascular risk . There is an inverse, graded, independent, and robust association between fitness and mortality risk in apparently healthy people, as well as in patients with CHD, irrespective of age, sex, or co-morbidities.

Mortality risk is highest for patients with low fitness. Risk decreases as fitness increases, irrespective of presence of other risk factors or age.

Little data are available regarding the combined health benefits of statins and fitness.

This prospective cohort study assessed the effects of statin treatment + exercise capacity (fitness) vs exercise capacity alone on all-cause mortality in veterans with dyslipidemia.

STUDY

1. A cohort was taken from a database of over 20 000 veterans who had dyslipidemia and a symptom-limited exercise tolerance test between 1998 and 2011.
2. None had history of implanted pacemaker, development of left bundle branch block during the test, inability to complete the test because of musculo-skeletal pain or impairment, exercise capacity less than 2 METs, or body mass index less than 15.5.
3. Created 4 categories of fitness on the basis of peak METs on the treadmill:
(One MET designates the amount of oxygen consumed at rest. Ed.)

5.0 METs and less	Lowest fit	(Lowest 25 percentile)
5.1 to 7.0 METs	Moderately fit	(26 th to 50 th percentile)
7.1 to 9.0	Fit	(51 -75 th percentile)
Above 9.0	Highly fit	(Over 75 th percentile)
4. Primary endpoint = death from any cause

RESULTS

1. Enrolled 10 043 middle-aged veterans (343 women). Median follow-up was 10 years during which 2318 (23%) died.
2. Baseline characteristics (Means or %):

A. Age 58; history of CHD 42; hypertension 55; current smoker 22; type 2 diabetes 38; taking beta-blocker 15; taking aspirin 7.

B. Lipids:

Total cholesterol 233 mg/dL

LDL-cholesterol 158 mg/dL

(Indeed, a high-risk, dyslipidemia cohort. I can't imagine why so many continued to smoke, and so few were taking aspirin. Ed.)

3. The numbers taking statins and the numbers not taking statins were about equal.

4. Taking statins:

Median duration of statin treatment was 70 months

Reduced total cholesterol from 235 to 169 (reduction of 66 mg/dL) and a reduced LDL-c from 154 to 138 (reduction of 16 mg/dL).

As fitness increased, mortality decreased from 37% to 6%.

Had a lower mortality than those not treated—18.5% vs 27.7%. (Adjusted) \

For each 1 MET increase in exercise capacity, mortality decreased by 12%.

(HR = 0.88).

Statins + fitness was related to fewer deaths than fitness-alone (12% vs 24%).

Mortality by fitness level:

	Number	Deaths (n ; %)	HR*
Least fit	1060	389 (37)	1.00 (Referent)
Moderately fit	1573	329 (21)	0.65
Fit	1705	173 (10)	0.40
Highly fit	<u>694</u>	<u>9</u> (<u>6</u>)	0.30
	5032	640 (12.7)	

(* Fully adjusted)

5. No statin (fitness alone):

Had a higher mortality than those treated with statins—24% vs 12%.

Mortality risks were significantly higher for all fitness groups not treated with statins vs those treated with statins.

For each 1 MET increase in exercise capacity, mortality decreased (HR = 0.89).

Mortality by fitness level:

Number	Deaths (n ; %)	HR*
--------	----------------	-----

Least fit	1024	531	(52)	1.36*
Moderately fit	1154	397	(34)	1.02
Fit	1335	270	(20)	0.81
Highly fit	<u>1498</u>	<u>190</u>	(13)	0.53
	5011	1386	(24.7)	

* Compared with 1.00 HR in those taking statins. .

DISCUSSION

1. Both statin treatment and increased fitness lower mortality significantly and independently from other clinical characteristics.
2. The study offers some unique and clinically relevant information:

Combined statin + exercise capacity greater than 5 METs lowers mortality risk substantially more than either alone.

The most unfavorable combination was low exercise capacity and lack of statin therapy. The most factorable combination was high fitness + statin treatment.

Combining moderate fitness with statin therapy offers additional protection against premature mortality in individuals with dyslipidemia.

Low fitness, absence of statin, or both, significantly increased risk of mortality.

For patients who cannot tolerate statins, achieving fitness of 7.1 to 9.0 METs offers modest protection against premature mortality.

For those with exercise capacity of more than 9.0 METs, protection against premature mortality was at least as much (if not greater) than that for individuals in the lowest and moderate fit range (5.1 to 7.0 METs) who were taking statins.

Physical activity, which improves fitness, is an efficacious and cost-effective way to prevent premature mortality and should be promoted by health care providers.

The low exercise capacity (roughly 7.0 METs) associated with health benefits is clinically significant and reinforces the importance of physical activity for individuals with dyslipidemia.

CONCLUSION

Statin treatment and increasing fitness were independently associated with lower mortality among dyslipidemic individuals. The combination substantially lowers mortality risk than either alone, reinforcing the importance of physical activity for middle-aged individuals with dyslipidemia.

These findings suggest that fitness is an attractive adjunct treatment to statins, or an alternative to those who cannot take statins.

Lancet February 2, 2013; 381: 394-99 Original investigation, first author Peter F Kokkinos, VA Medical Center, Washington DC and Georgetown University School of Medicine

An editorial in this issue of Lancet (p 356) first author Pedro C Hallal, Federal University of Pelotas, Brazil comments and expands on the article.

Fitness associated with significantly lower all-cause mortality can be achieved through moderate-to-vigorous physical activity, including walking, gardening, participation in gym classes, and sport.

Evidence from the Cooper Institute indicates that 20th percentile of fitness among healthy men aged 55-64 corresponds to 8.9 METs. In the preceding study, a population with a mean age of 58, any level of fitness above 5 METS (equivalent to light cycling) was associated with lower mortality regardless of statin treatment.

The cost of becoming physically active is probably lower than the cost of drugs. Moderate physical activity has few adverse effects. It should be part of everyday life.

Not all patients with dyslipidemia will be prescribed statins, and not all patients who receive a prescription will take them.

Physical activity is undervalued in primary care practice. Many patients have never received a prescription for increasing physical activity. Such a prescription should be on par with drug prescription.

Prescription of physical activity alone will not ensure that the patient will become physically active. However, doctors continue to prescribe drugs. They should also continue to prescribe physical activity as a routine part of practice.

The message: fitness per se is beneficial.

I can easily apply these conclusions to patients without dyslipidemia, to women, and to all ages.

Can a 58 year old, whose fitness is low, benefit from beginning a fitness program and increasing fitness level? I believe so.

The benefit / harm –cost ratio of maintaining fitness or achieving fitness is very high.

The more I study the current literature, the more I believe that the major activity of primary care medicine is to foster healthy lifestyles.

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Fitness—A Reliable Prescription For Dementia Prevention.

[2-4] NEVER TOO FIT FOR BODY AND MIND

(This editorial comments on the preceding article Ed.

There is a tidal wave of evidence about the benefits of physical fitness across the lifespan, including benefits on cognition, and prevention of dementia.

The evidence comes in many forms: Epidemiological studies, clinical trials, and in vitro and in vivo biological studies implicating neuro-mechanisms affected by aerobic activity.

The beneficial effect of fitness seems to be independent from, and perhaps greater than, many other factors such as diabetes and hypertension control. Greater reduction in mortality risk has been noted in fit persons than in the unfit regardless of body mass index. In fact, fit overweight persons have a lower risk for death than the unfit normal-weight person.

Previous studies have described:

The benefit of fitness on cognition among those with co-morbid conditions, such as obesity and diabetes.

Midlife health and behaviors can influence future outcomes. Midlife depression, smoking, high BMI, and other cardiovascular risk factors increase the risk of dementia in later life. Modification of these factors may reduce risk of dementia.

Fitness and PA have been shown to affect dementia-related mortality.

Cognition, as well as dementia, immediately and remotely, have been associated with physical activity.

The preceding study confirms previous observations. Cardio-respiratory testing adds some conviction to the association. Even in healthy cohorts, higher fitness levels yield greater protection against dementia.

It is interesting that the association of fitness with reduced risk of dementia exists in “super-healthy” persons as well as those with co-morbid conditions.

There may be a dose-response relationship between fitness and cognitive health.

Health behaviors are often long-standing. In a large cohort of women, self-reported PA in adolescence corresponded with the likelihood of being physically active later in life. PA in early adolescent years has been associated with greater reduction in risk of dementia. Behaviors established in early life may persist.

Unfortunately, adherence to exercise regimens is notoriously difficult. Behavioral changes are most likely to occur in the face of health problems.

Given that PA is associated with lower risk of cognitive decline, and the relative safety of the intervention, PA seems to be a reliable prescription for dementia prevention.

Annals Internal Medicine February 5, 2013; 158: 213-14 Editorial by Mary Sano, Mount Sinai School of Medicine, New York..

Important advice—start fitness programs early in life.

The study compared fit persons with more fit persons. Primary care would consider unfit persons with moderately fit persons. Encouraging unfit patients to a greater degree of fitness should be a continuing effort of primary care clinicians.

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Use Of Prenatal FA Supplements Around The Time Of Conception Was Associated With A Lower Risk Of Autistic Disorder.

[2-5] ASSOCIATION BETWEEN MATERNAL USE OF FOLIC ACID SUPPLEMENTS AND RISK OF AUTISM SPECTRUM DISORDERS IN CHILDREN

Supplementation with folic acid (FA) around the time of conception reduces risk of neural tube defects. This has led to mandatory fortification of flour with FA. It is generally recommended that women planning pregnancy take a daily supplement of FA starting 1 month before conception.

There also is evidence that FA supplementation during pregnancy may be associated with reduced risk of other neuro-developmental disorders in children. A recent study of 38 954 children in Norway found that maternal intake of FA supplements from 4 weeks before to 8 weeks after start of pregnancy was associated with lower risk of severe language delay at 3 years. A case-control study from California reported that maternal intake of FA during the 3 months prior to pregnancy and the 1st month of pregnancy was associated with a lower risk of autism spectrum disorders (ASD). This may have been modified by gene variants that determine the ability to utilize available FA.

This study investigated the association between maternal use of FA supplements in early pregnancy and subsequent risk of ASD: Autistic disorder (AD), Asperger syndrome, and pervasive developmental disorder—not otherwise specified. (PDD-NOS)

STUDY

1. Included 85 176 children born in 2002-2008 derived from a population-based prospective Norwegian study.

2. By the end of the follow-up (2012) the age range of the children was 3.3 to 10.2 years. (Mean = 6.4 years)
3. The exposure of primary interest was use of FA from 4 weeks before to 8 weeks after the start of pregnancy.
4. Main outcome measure = confirmed diagnosis of ASD.
5. Measures of ASD:

Cases of ASD were identified through: 1) questionnaire screening of mothers at offspring ages 36 months, 5 years, and 7 years; 2) referral of children suspected of having ASD; and 3) linkage to a Norwegian Registry.

When a child with ASD or potential ASD was detected he or she was invited to participate in a clinical assessment that included the standard instruments for diagnosis of ASD. Diagnoses were based on DSM-IV.

6. Measures of FA use and dietary folate intake.

Since 1998, the Norwegian Directorate of Health has recommended that all women attempting to become pregnant should take a 400 ug FA supplement daily for 1 month before conception through the first trimester. (Multivitamin supplements at the time this study was started contained less than 400 ug.)

Detailed information about mother's supplement intake was obtained by questionnaire reported at 18 weeks of gestation. No foods were fortified with FA. Additional information about supplement and dietary intake was obtained from a food frequency questionnaire completed in week 22. Women were asked to write the name of supplements they were currently taking (in week 22) and exact amounts of vitamins and minerals were calculated.

7. Measures of timing:

For the primary analysis the study used an interval from 4 weeks before to 8 weeks after start of pregnancy. (The exposure period)

Children of mothers who used FA supplements during the entire or part of exposure period were compared with children whose mothers did not use FA supplements during the interval.

The exposure period was chosen on the basis of an hypothesis that the effect of FA on the development of the central nervous system is most prominent during this period. It corresponds to the interval used in previous study of language delay. The interval covers events of critical importance to the fetal brain, such as closure of the neural tube and basic brain structures.

RESULTS

1. To isolate FA exposure from other exposures reported to increase risk of ASD, the study excluded children with gestational age less than 32 weeks at birth, those weighing less than 2500 g, and multiple births.
2. The final study sample included 85 176 children.
3. Proportion of mothers reporting use of FA:

Weeks 4 to 1 before start of pregnancy	32%
Weeks 9 through 12	71%
Weeks 13 through 16	46%
4. A total of 270 children (0.32%) were diagnosed with ASD:

Autistic disorder	114 (0.13%)
Asperger syndrome	56 (0.07%)
PDD-NOS	100 (0.12%)
5. Women who used FA within 4 weeks before to 8 weeks after start of pregnancy were more likely to have higher education levels, to have planned the pregnancy, to be non-smokers, to have BMI below 25, and be first-time mothers.
FA use increased substantially by year of birth: 43% for 2002 and 83% in 2008
6. There was an inverse association between FA use and subsequent risk of autistic disorder:

	AD present
Mothers took FA	0.10% (64 of 61 042)
Mothers did not take FA	0.21% (50 of 24 134)

Odds ration (OR) of AD = 0.61 (takers vs non-takers).
(Adjusted for year of birth, maternal education level, and parity.)
7. Although fish oil intake followed a similar pattern, there was no associating with risk of AD.
8. The inverse association found for FA use in early pregnancy was absent for FA use in mid pregnancy (OR = 0.96)
9. For Asperger syndrome, the proportion of diagnosed cases was 0.12% (21/17 218) in FA users, and 0.21% in non-users (27/12899)—adjusted odds ratio = 0.65. However, the power to detect an odds ratio similar to that found for AD (0.61) was limited.
10. For PDD-NOS, the adjusted OR was 1.04. (No association)
11. The use of of other vitamins and minerals did not appear to affect risk of

AD. The analysis in which cases were stratified according to language level suggested that the inverse association may be stronger in children with severe language delay and weaker in those with moderate or no delay.

DISCUSSION

1. Maternal use of supplemental FA 4 weeks before to 8 weeks after the start of pregnancy was associated with a lower risk of autistic disorder—the most severe form of ASD—in children.
2. The investigators could not exclude the possibility that some portion of the inverse association represents residual unmeasured confounding. However, if residual confounding was substantial, a lower risk would have been expected associated with fish oil supplement use as well, because the fish oil use was associated with the same parental characteristics as the study sample.
3. The inverse association may be largely driven by the children with AD and severe language delay at 36 months. These are the more severely affected children.
4. Mothers in the cohort were more likely to be first-time mothers, less likely to be single mothers, and have higher education levels, higher mean age, and lower levels of smoking than other pregnant women.
5. Under-assessment was less of a problem for autistic disorder than for other ASD types, but it was reassuring that the inverse association for autistic disorder was stronger in older children (born in 2002-2004), for whom case ascertainment was close to complete.
6. A limitation of the study was the reliance on subtype diagnoses. Subtype diagnoses of ASD have been found not to have high reliability, and may be removed from the upcoming DSM-V classification system.
7. The finding of an inverse relationship between use of FA around the time of conception and lower risk of autistic disorder does not establish a causal relationship, but provides a rationale for replicating the analyses and further investigation of genetic factors and other biological mechanisms that may explain the inverse association.

CONCLUSION AND RELEVANCE

Use of prenatal FA supplements around the time of conception was associated with a lower risk of autistic disorder.

These findings support prenatal use of FA supplementation.

JANA February 13, 2013; 309: 570-77 Original investigation, first author Pal Siren Norwegian Institute of Public Health, Oslo

If this relationship between FA supplementation and Ad turns out to be true, it will be a major advance.

AD is devastating to the child, the family, and to society. Preventing even one case would be a therapeutic triumph.

Primary care clinicians are not often concerned about things obstetrical. However, in regard to prevention of AD, they must be involved. We include many female patients of reproductive age in our practices. If FA supplements do indeed reduce incidence of AD by 50%, we must make a decision about who to treat. All women in this category? Select patients?

Fortunately, the denominator of the benefit / harm-cost ratio of FA is very low. Harms are nil.

Until more certain information is available, I would be very generous in advising FA supplements for almost every female patient of reproductive age.

In The US, The Average Daily Intake Of FA Is Approximately 150 Ug From Food Fortified By FA.

[2-6] PERI-CONCEPTIONAL FOLIC ACID AND RISK OF AUTISM SPECTRUM DISORDER

(This editorial comments and expands on the previous article.)

Autism spectrum disorders (ASD) are a group of neuro-developmental disorders characterized by impairment in social interaction and communication, and by repetitive restrictive and stereotyped patterns of behavior.

The most serious of the conditions comprising ASD is autistic disorder (AD), because it is likely to co-occur with intellectual disability, and a range of medical, behavioral, and psychiatric complications.

Prevalence of ASD is estimated to be approximately 1% of children. Because of increasing temporal trends in autism prevalence, and the clinical and behavioral challenges of the condition, understanding the risk factors, determining potential causes and prevention, and evaluating treatment options, are high priorities.

Although ASD is heritable, the clinical presentation can vary widely between family members and among infected individuals. Genetic factors are the best studied risk factors so far identified. Some

prenatal, obstetric, and environmental exposures (parental age, parental drug exposure, and infections) have been associated with increased risk for ASD.

Heterogeneity is a major obstacle to researchers. Identified risk factors are implicated in only a minority of cases. The etiology of ASD remains largely unknown.

FA (a synthetic stable form of folate) affects basic cellular processes, including DNA, RNA, and protein metabolism. It is biologically plausible that FA intake might affect numerous conditions negatively or positively, depending on timing and dose.

It is important to confirm the finding of the study in other population-based birth cohorts.

In the US, the average daily intake of FA is approximately 150 ug from food fortified by FA.

The potential for a nutritional supplement to reduce the risk of autistic disorder is provocative and should be confirmed in other populations.

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