# Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies

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## STUDY QUESTION

What is the relation between intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer?

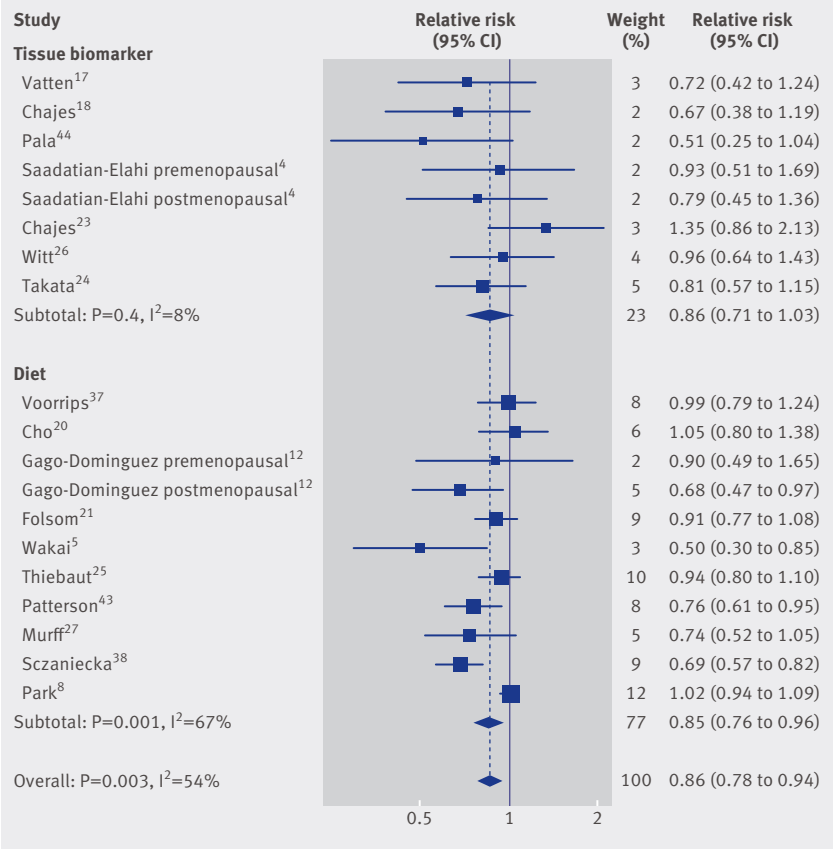
## SUMMARY ANSWER

High intake of marine n-3 polyunsaturated fatty acids is associated with 14% reduction of breast cancer risk, and risk of breast cancer is reduced by 5% per 0.1 g/day or 0.1% energy/day increment of intake.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Results from prospective studies for fish and n-3 polyunsaturated fatty acids intake and risk of breast cancer are inconsistent. This study indicates that higher consumption of dietary marine n-3 polyunsaturated fatty acids, but not fish, is associated with a lower risk of breast cancer.

**Relative risk of breast cancer for highest versus lowest category of marine n-3 PUFA**




### Selection criteria for studies

We searched PubMed and Embase up to December 2012 and references of retrieved relevant articles and included prospective cohort studies that reported relative risks and 95% confidence intervals for breast cancer according fish intake, n-3 polyunsaturated fatty acids intake, or tissue biomarkers.

### Primary outcome

Incident breast cancer in women.

### Main results and role of chance

Twenty six publications, including 20 905 breast cancer cases and 883 585 participants from 21 independent prospective cohort studies were eligible. Intake of marine n-3 polyunsaturated fatty acids was associated with 14% reduction of breast cancer risk (highest versus lowest category, relative risk 0.86, 95% confidence interval 0.78 to 0.94, $I^2$=54), and the relative risk remained similar whether marine n-3 polyunsaturated fatty acids was measured as dietary intake (0.85, 0.76 to 0.96, $I^2$=67%) or as tissue biomarkers (0.86, 0.71 to 1.03, $I^2$=8%). Dose-response analysis indicated that the risk of breast cancer was reduced by 5% per 0.1g/day (0.95, 0.90 to 1.00, $I^2$=52%) or 0.1% energy/day (0.95, 0.90 to 1.00, $I^2$=79%) increment of intake. No significant association was observed for fish intake or alpha linolenic acid exposure.

### Bias, confounding, and other reasons for caution

The inverse association between marine n-3 polyunsaturated fatty acids and risk of breast cancer became more evident in studies that had not adjusted for body mass index (BMI) and became marginally significant in studies that had adjusted for BMI. This indicated an important role of body fat for the observed association. The null association observed for fish intake and the discrepancy for risk of breast cancer between fish and marine n-3 polyunsaturated fatty acids might be because of the low fish intake together with a high use of fish oil supplementation in some North American and European countries. Other constituents in fish, such as organometallics and pesticides, could attenuate the protective effect of fish on breast cancer.

### Study funding

The study was funded by the National Natural Science Foundation of China (NSFC, No 81273054), the PhD Programs Foundation of Ministry of Education of China (20120101110107), and the National Basic Research Program of China (973 Program 2011CB504002).

# Care in specialist medical and mental health unit compared with standard care for older people with cognitive impairment admitted to general hospital: randomised controlled trial (NIHR TEAM trial)

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Clinical review: Cognitive assessment of older people (*BMJ* 2011;343:d5042)

## STUDY QUESTION

Does a specialist medical and mental health unit (MMHU) improve outcomes, experience, and satisfaction for older people with dementia or delirium admitted to an acute hosptial compared with standard care?

## SUMMARY ANSWER

Days spent at home, health status, and service use were no different between settings, but the experience of patients and satisfaction of family carers improved.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Specialist units have been proposed to improve outcomes and experience for people with cognitive impairment admitted to hospital and to reduce health and social services resource use. With a specialist medical and mental health unit we did not find improved health status or reduced service use, but the experience of patients and satisfaction of family carers were improved. These outcomes are important, in particular as many of these patients were approaching the end of life.

### Design

A randomised controlled trial compared a specialist medical and mental health unit, providing best practice care, with standard hospital wards. Allocation was via a website, in a permuted block design. Patients' experience was ascertained by structured non-participant observations. Otherwise outcome data collection was blind to allocation.

### Participants and setting

Six hundred participants aged over 65 admitted to a large NHS general hospital for acute medical care, identified on admission as "confused."

**Outcome in patients with cognitive impairment admitted to specialist medical and mental health unit (MMHU) or standard care**

| | MMHU (n=310) | Standard care (n=290) | Difference (95% CI) |
|---|---|---|---|
| Median (IQR) days at home | 51 (0-79) | 45 (0-78) | 6 (−12 to 24) |
| Mortality | 68 (22%) | 71 (25%) | 1.0* (0.7 to 1.3) |
| Return home | 228 (74%) | 202 (70%) | 0.9* (0.6 to 1.3) |
| Readmitted | 99 (32%) | 101 (35%) | 0.8* (0.6 to 1.2) |
| New care home placement | 45/222 (20%) | 65/230 (28%) | 0.8* (0.5 to 1.2) |
| Positive mood or engagement (% of 5 min observation periods) | 79% | 68% | 11% (2% to 20%) |
| Median (IQR) personal enhancers/observation | 4 (1-8) | 1 (0-3) | 3 (1 to 5) |
| Median (IQR) personal detractors/observation | 4 (2-7) | 5.5 (3-10.5) | −1.5 (−5 to 1) |
| Carer mostly or very satisfied with care overall | 214/234 (91%) | 189/228 (83%) | 8% (2% to 15%) |

IQR=interquartile range.
*Adjusted odds ratio.

### Primary outcome

Days spent at home (or in the same care home) in the 90 days after randomisation, patients' experience by direct observation, satisfaction of family carers with care by telephone interview.

### Main results and the role of chance

There was no significant difference in the number of days spent at home (median 51 *v* 45 days, 95% confidence interval for difference −12 to 24; P=0.3). The median index hospital stay was 11 versus 11 days, mortality 22% versus 25% (−9% to 4%), readmission 32% versus 35% (−10% to 5%), and new admission to a care home 20% versus 28% (−16% to 0), for the specialist unit and standard care, respectively. Participants on the specialist unit spent significantly more time in a positive mood (79% *v* 68%, 2% to 20%; P=0.03) and experienced more staff interactions that met emotional and psychological needs (median 4 *v* 1 per observation; P<0.001). More family carers were satisfied with care (overall 91% *v* 83%, 2% to 15%; P=0.004), and severe dissatisfaction was reduced (5% *v* 10%, −10% to 0%; P=0.05).

### Harms

Inpatient falls were more frequent on the specialist unit (27% *v* 18%, −2% to 20%; P=0.10).

### Bias, confounding, and other reasons for caution

A Zelen-type design was necessary to accommodate the demands of a busy acute medical admission system, resulting in imbalances in some baseline variables that were associated with outcomes (delirium prevalence 53% *v* 62%; previous residence in care home 28% *v* 21%). These were adjusted for statistically. Some 70% of "standard care" was on specialist geriatric medical wards, although process of care was documented to be different between settings. Statistical power to detect moderate differences in outcomes was limited.

### Generalisability to other populations

The study took place in a single UK centre, which provided sole acute hospital medical services for its population. Results should be generalisable to similar hospitals, but require replication.

### Study funding

The study was funded by the National Institute for Health Research.

### Trial registration number

Clinical Trials NCT01136148

# Systematic identification and treatment of smokers by hospital based cessation practitioners in a secondary care setting: cluster randomised controlled trial

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## STUDY QUESTION

Can the systematic default provision of smoking cessation support to all adult smokers admitted to hospital increase the number of smokers who quit smoking after admission?

## SUMMARY ANSWER

Relative to usual care, delivering behavioural support and pharmacotherapy to smokers admitted to hospital by default substantially increases uptake of the intervention, increases referral to and uptake of community support after discharge, and doubles validated cessation of smoking at four weeks after discharge.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Evidence based interventions for smoking cessation are effective and highly cost effective, but delivery in hospital is far from comprehensive. This study shows that delivering evidence based services by default, while in hospital, increases service uptake and rates of smoking cessation; therefore, wider adoption of this approach could make a substantial contribution to individual and population health.

### Design

Open, cluster randomised controlled trial (ISRCTN25441641.). Smokers were cluster randomised by admission ward to receive either usual care (cessation interventions at the discretion of their clinical staff) or systematic ascertainment and delivery of behavioural support and pharmacotherapy (usually combination nicotine replacement therapy) at the bedside. The intervention commenced as soon as possible after admission, with follow-up delivered either by the hospital team or through referral to a local stop smoking service, according to patient preference.

### Participants and setting

The study included 493 patients admitted to acute medical wards in a large teaching hospital in the United Kingdom's health service (264 intervention, 229 usual care). Primary outcome data were available at four weeks for 260 and 224 patients given the intervention and usual care, respectively; those lost to follow-up were assumed to have relapsed to smoking.

### Primary outcome(s)

Smoking cessation at four weeks, validated by measuring levels of exhaled carbon monoxide. Secondary outcomes included uptake of inpatient behavioural support, use of cessation pharmacotherapy, referral to and uptake of community support after discharge, and validated smoking cessation at six months. Odds ratios were adjusted for the cluster design of the trial and for the stratification variable (high *v* low discharge rate; >10 *v* ≤10 patients per week, respectively).

### Main results and the role of chance

All patients in the intervention group received at least brief advice to quit smoking compared with 106 (46%) patients in the usual care group. Cessation at four weeks was achieved by 38% (n=98) of intervention and 17% (n=37) of usual care patients (adjusted odds ratio 2.10 (95% confidence interval 0.96 to 4.61), P=0.06, number needed to treat 8). Uptake of behavioural support, use of pharmacotherapy, and referral to and uptake of community support after discharge were all higher in the intervention group than in the usual care group. Cessation at six months was also higher in for the intervention than for usual care, although this difference was not significant (19% *v* 9%; adjusted odds ratio 1.53 (95% confidence interval 0.60 to 3.91)). No harms were evident throughout the study.

### Bias, confounding, and other reasons for caution

Cluster randomisation by ward precluded analysis of effects within wards or medical specialties, but published evidence suggests that admission diagnosis is not a major determinant of smoking cessation. There was no allocation concealment, but patients were admitted to wards according to sex and specialty; therefore, selection bias in relation to the intervention is unlikely. Provision of information about the trial might have increased cessation in the usual care group, but this would reduce the apparent difference in treatment effects.

### Generalisability to other populations

The study was carried out in a single centre for logistical reasons, but the increased cessation observed is likely to generalise to any centre not currently offering cessation support at default.

**Key study outcomes based on nine clusters (wards) in each randomised group**

| | Eligible population (%) | | Adjusted odds ratio (95% CI) | P |
|---|---|---|---|---|
| | Usual care | Intervention | | |
| Primary outcome | | | | |
| Quit at four weeks (continuous abstinence) | 17 (n=37) | 38 (n=98) | 2.10 (0.96 to 4.61) | — |
| Secondary outcomes | | | | |
| Offered behavioural support or pharmacotherapy as an inpatient | 46 (n=106) | 100 (n=264) | NA | — |
| Accepted behavioural support as an inpatient | 29 (n=17) | 70 (n=185) | 5.71 (3.58 to 9.09)* | <0.001 |
| Discharged with any pharmacotherapy for smoking cessation | 27 (n=62) | 49 (n=128) | 3.95 (1.81 to 8.63) | <0.001 |
| Referral to a stop smoking service after discharge | 6 (n=13) | 55 (n=144) | 21.8 (9.4 to 50.6) | <0.001 |
| Received support from a stop smoking service after discharge | 10 (n=21) | 31 (n=80) | 4.22 (2.27 to 7.83)† | <0.001 |

NA=not applicable.
*Logistic regression model with adjustment for stratification variable allowing for the cluster design of the trial using robust standard errors.
†Model excluded the stratification variable as random effect not estimable.

# Fertility treatment and risk of childhood and adolescent mental disorders: register based cohort study

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## STUDY QUESTION

Do children conceived after fertility treatment have higher, comparable, or lower risk of mental disorders in childhood or adolescence compared with children born after spontaneous conception?

## SUMMARY ANSWER

There was an increased risk of mental disorders in children born after ovulation induction/intrauterine insemination, while children born after in vitro fertilisation or intracytoplasmic sperm injection (IVF/ICSI) had a similar overall risk to children conceived spontaneously.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Children born after fertility treatment have an increased risk of some perinatal outcomes, though long term development has been sparsely investigated and few have studied children born after induced ovulation. Though the overall long term development of children born after IVF/ICSI is comparable with that of children conceived spontaneously, children born after induced ovulation seem to have a small increased risk of autism, hyperkinetic disorders, conduct, emotional or social disorder, and tic disorders, but the absolute risks are low.

### Participants and setting

Participants in this study were all children born between 1995 and 2003 in Denmark.

### Design, size, and duration

This population based cohort study included 588 967 children with follow-up in 2012 when the children were aged 8-17. Information was obtained from Danish national health registers and linked with the unique Danish personal identification number.

### Main results and the role of chance

The absolute risk of any of the included mental disorders was 3.9% among children born after spontaneous conception, 3.5% in IVF/ICSI children, and 4.1% in children born after ovulation induction/intrauterine insemination. The risk of mental disorders in children born after IVF/ICSI compared with spontaneously conceived children was not increased, except for a borderline significant increased risk of tic disorders (hazard ratio 1.4, 95% confidence interval 1.0 to 1.9, absolute risk 0.3%). By contrast, children born after ovulation induction/intrauterine insemination had small but significantly increased risks of any mental disorder (1.2, 1.1 to 1.3; absolute risk 4.1%), autism spectrum disorders (1.2, 1.1 to 1.4; 1.5%), hyperkinetic disorders (1.2, 1.1 to 1.4; 1.7%), conduct, emotional, or social disorder (1.2, 1.0 to 1.5; 0.8%), and tic disorders (1.5, 1.2 to 2.0; 0.4%). There was no systematic risk related to any specific type of hormonal drug treatment.

### Bias, confounding, and other reasons for caution

Although Danish national health registers are considered a source of high quality data covering the entire population, no registers are complete. Analyses were adjusted for maternal age, parity, educational level, smoking in pregnancy, psychiatric history, birth year, child's sex, and multiplicity. We cannot, however, rule out residual confounding.

While IVF/ICSI is more complex than ovulation induction/intrauterine insemination and includes both hormonal stimulation and in vitro manipulation of gametes, we found no relation with IVF/ICSI but instead an association with ovulation induction/intrauterine insemination, which includes hormonal treatment alone. The specific hormonal treatments differ mainly by the use of clomiphene citrate in induced ovulation. As we found no association with the use of this drug, the increased risk might not originate from the treatment but rather from underlying causes of parental subfertility in the ovulation induction/intrauterine insemination group.

### Generalisability to other populations

The mechanisms of adverse effects related to fertility treatment or subfertility in the parents are not completely understood. The associations found in this study might therefore not be applicable in other populations where availability and procedures of fertility treatment are different.

**Method of conception and hazard ratios for mental disorders in children, Denmark 1995-2012**