Reviewer's report

Title: Dietary intake of fish, omega-3, omega-6 polyunsaturated fatty acids and vitamin D and risk of psychotic-like symptoms in a cohort of 33 000 women from the general population

Version: 1 Date: 4 January 2010

Reviewer: Jessica Sontrop

Reviewer's report:

MAJOR COMPULSORY REVISIONS

1. Introduction:

Evidence is presented to support a link between PUFAs and schizophrenia, but the authors need to clarify how the outcome of their study fits into the causal hypothesis. For instance, is there a temporal relationship between these three conditions (eg do these three phenomena represent a continuum or is schizophrenia often preceded by milder symptomatology or delusional ideation, or some combination thereof?). Do these conditions have a distinct onset and remain relatively constant thereafter, or can they be isolated events? What is known about the typical age of onset of the outcome, delusional ideation and schizophrenia?

2. Title and Objectives:

The authors' stated objective is to evaluate the association between dietary intake of PUFAs (n3 and n6) and vitamin D and the risk of positive psychotic-like symptoms from diet.

Use of the term risk implies that only new (incident) cases with the outcome (psychotic-like symptoms) were measured. However, dietary intake was measured on one occasion at baseline (1991-2) and the outcome was measured on one occasion in a follow-up survey approximately 10 years later (2002-3). Since psychotic symptoms were not measured in the baseline survey (and so prevalent cases were not excluded), the outcome is a measure of prevalence, not incidence, and therefore it is not possible to evaluate the risk of the outcome since by definition, risk is a measure of incidence.

I suggest the statement of objectives in the intro and abstract be re-worded to: To evaluate the association between the prevalence of positive psychotic-like symptoms and previous intake of PUFAs (n3 and n6) and vitamin D measured 10 years earlier.

Similarly, the title could be re-worded to: Prevalence of positive psychotic-like symptoms in relation to previous intake of PUFAs and vitamin D measured 10 years earlier.
3. Methods

The study design, although described, is not defined. The study design does not appear to fit the criteria for standard study designs, although it may be defined as a retrospective population-based case-control study. It would be misleading to describe this study as a cohort study with dietary exposure measured at baseline followed by the outcome a decade later since participants who have the outcome at study entry are unknown and can't be excluded. Rather, participants with and without the outcome are identified, and then the researchers look back in time to see what proportion were exposed/unexposed. Since the outcome has three categories, the cases or controls may be divided into two groups of increasing or decreasing severity. This study could only be defined as a retrospective cohort study if there is strong evidence that development of the outcome rarely occurs before the age of 50 (which was the mean age of study participants at baseline).

4. Discussion:

Given the j-shaped relationship observed between the outcome and dietary intake of vit D and PUFAs, the first paragraph of this discussion describing a protective effect on the outcome with “increasing” dietary intake of PUFA and vitD is highly misleading (a greater intake of fatty fish was associated with the highest level of positive psychotic-like symptoms).

Moreover, given that the outcome is a measure of prevalence that could theoretically precede the dietary exposure, it is not possible to draw any conclusions regarding temporality or causation. It is possible that the outcome itself determines preference for dietary items with higher or lower PUFA or vit D – “a protective effect” of these foods cannot be claimed based on these data.

5. Limitations:

It is not clear that a single measure of dietary intake is sufficient to categorize participants into exposure categories which are then used to predict an outcome variable measured 10 years later. The references provided in the discussion to support the “stability of dietary patterns from year to year” is vague and is not specific to PUFAs or vitamin D. This is an important limitation and should be discussed further with an emphasis on how it might be corrected in future research.

For example, please discuss the difficulties and implications of measuring an exposure that may vary over time. Greater discussion of issues related to exposure intensity and duration with respect to the causal hypothesis would be informative. Is there a hypothesized induction time? If the exposure ceases is the effect of exposure thought to continue? Does it matter whether exposure is acute or chronic?

Assuming that it is the biological availability of PUFAs and vit D that is related to the outcome under study, the authors should provide greater detail on how well intake of PUFAs and vit D correlates with biological availability once consumed.
For instance, linoleic acid and alpha-linolenic acid compete for the same desaturase and elongase enzyme systems and a high intake of LA relative to ALA can inhibit the synthesis of EPA and DHA by competitive inhibition.

How well does vitamin D intake correlate with serum levels? Is information available on vit D supplementation?

The authors should provide additional discussion about the hypothesized relationship between PUFAs and schizophrenia. Is the association simply due to a dietary deficiency, which can be remedied by supplementation or is it one of faulty metabolism, which may not respond to supplementation? Is it hypothesized that all people with diets deficient in PUFAs will be at greater risk for schizophrenia? Or just some? What might make some individuals susceptible and others not?

Discuss the difficulties and implications of capturing an outcome such as positive-like psychotic symptoms which may have an ambiguous onset and variable duration. How might this be improved on in future research? Is information available on whether participants were receiving pharmacologic treatment for the outcome?

Greater consideration of confounding is required. What is the potential for unmeasured or residual confounding?

6. General comments:

Since the outcome measure in this study is a measure of prevalence not incidence, the use of the term “risk” should be removed from all parts of the manuscript including the abstract, title, objectives, and conclusions, unless it is used to refer to a “risk-factor”. The terms odds, prevalence or proportion should be used as appropriate. Given that temporality cannot be established, all references to the “protective effect” of PUFAs or vitamin D should be removed (unless referring to the results of previous research with clear temporality).

It is not possible to draw any conclusions regarding causation in this study. At most, it may be concluded that dietary intake of PUFA and vitamin D are inversely correlated in a j-shaped pattern with the outcome; however, it is not possible to draw conclusions about the direction of this relationship.

MINOR DISCRETIONARY REVISIONS

7. Introduction

The introduction would be improved by including a critical appraisal of the studies discussed (eg, should evidence from an ecological study be given the same weight as evidence from a clinical trial?)

On page 5, the sentence describing a “positive effect on their mental state” is vague. What was the magnitude and significance of the effect (was the effect clinically and statistically significant)? What is meant by the term “mental state”?
8. Methods:

The authors define the outcome as the presence of positive psychotic-like symptoms. This outcome measure was based on 20 questions on positive psychotic-like symptoms from a questionnaire called CAPE (Community Assessment of Psychic Experiences), which was derived from a modified version of the Peters et al. Delusions Inventory (PDI). A reference with psychometric statistics for the PDI is provided in the methods section. Information and references on the validity of CAPE, which are currently in the discussion section, should be moved to the methods section. The psychometric properties of the outcome measure should be provided in the methods. It is not clear whether this scale has been validated in the Swedish population (e.g., in some cultural backgrounds it may be more or less acceptable to hold certain views such as belief in the telepathy or the paranormal). Based on the information currently provided, it is not clear that the outcome variable is a valid measure of positive-like psychotic symptoms. Most psychometric scales rely on validated cut-points, and it is not clear that the cut-points used for this outcome measure are valid.

How were missing data handled in the analyses? Please provide the available sample size for the multivariable analyses.

9. Results:

Please report the effect measures as odds ratios, not relative risks.

10. Discussion:

How do intakes of PUFAs and vit D in this cohort compare to other populations? How might this affect the generalizability of the results? Perhaps vitamin D intake is more important in a climate with longer winters and less sun exposure?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.