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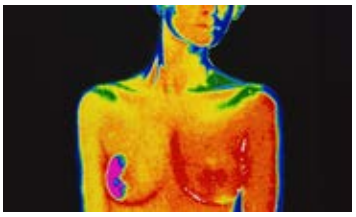

Increased risk of venous thromboembolism in tamoxifen users p 101

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ORIGINAL RESEARCH Systematic review

Long term adjuvant endocrine therapy and risk of cardiovascular disease in female breast cancer survivors

Matthews A, Stanway S, Farmer RE, et al

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Study question What is the effect of endocrine therapies on a range of specific cardiovascular disease outcomes in women with a history of non-metastatic breast cancer?

Methods This systematic review and meta-analysis of randomised controlled trials (RCTs) and observational studies involved searching Medline and Embase for relevant papers up to June 2018. Studies were included if they investigated the risk of a specific cardiovascular disease outcome associated with either tamoxifen use or aromatase inhibitor use, or compared the two treatments, in women with a history of non-metastatic breast cancer.

Study answer and limitations 26 studies were identified, with results for seven specific cardiovascular disease outcomes (venous thromboembolism, myocardial infarction, stroke, angina, heart failure, arrhythmia, and peripheral vascular disease).

Overview of number of studies, direction of effect, and significant studies for selected outcome and comparison combinations

		No of studies		
Outcome	Comparison	Total	RR<1 (95% CI excluded 1)	RR≥1 (95% CI excluded 1)
Myocardial infarction	Aromatase inhibitor *v* tamoxifen	5	1 (0)	4 (2)
	Addition of tamoxifen	8	5 (3)	3 (0)
	Addition of aromatase inhibitors	2	2 (0)	0 (0)
Stroke	Aromatase inhibitor *v* tamoxifen	6	3 (1)	3 (1)
	Addition of tamoxifen	6	3 (1)	3 (0)
	Addition of aromatase inhibitors	2	1 (0)	1 (0)
Angina	Aromatase inhibitor *v* tamoxifen	1	0 (0)	1 (0)
	Addition of tamoxifen	2	2 (1)	0 (0)
	Addition of aromatase inhibitors	1	0 (0)	1 (1)
Venous thromboembolism	Aromatase inhibitor *v* tamoxifen	6	5 (4)	1 (0)
	Addition of tamoxifen	8	7 (3)	1 (0)
	Addition of aromatase inhibitors	1	0 (0)	1 (1)

RR=relative risk.

Results suggested an increased risk of venous thromboembolism in tamoxifen users compared with both non-users and aromatase inhibitor users. Results were also consistent with a higher risk of the vascular diseases myocardial infarction and angina in aromatase inhibitor users compared with tamoxifen users, but there was also a suggestion that this may be partly driven by a protective effect of tamoxifen on these outcomes. Some studies may have been missed owing to literature database restrictions, but multiple large databases were searched and manual searches of the included studies' reference lists and relevant meta-analyses were performed.

What this study adds This review has collated substantial RCT and observational evidence on the effect of endocrine therapies on several specific cardiovascular disease outcomes, progressing knowledge. The choice of aromatase inhibitor or tamoxifen will primarily be based on the effectiveness against recurrence of breast cancer, but this review shows that the individual patient's risk of venous or arterial vascular disease should be an important secondary consideration.

Competing interests, funding, and data sharing The Wellcome Trust and the Royal Society jointly funded this study. Competing interests are listed in full on bmj.com.
Systematic review registration Prospero CRD42017065944.

Omega 3 polyunsaturated fatty acids and healthy ageing

ORIGINAL RESEARCH Prospective cohort study

Serial circulating omega 3 polyunsaturated fatty acids and healthy ageing among older adults in the Cardiovascular Health Study

Lai HTM, de Oliveira Otto MC, Lemaitre RN, et al

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Study question Are higher long term levels of serially measured blood omega 3 polyunsaturated fatty acids (n3-PUFAs) associated with healthy ageing later in life?

Methods In a community based multicentre prospective US cohort, 2622 adults with a mean age of 74.4 (SD 4.8) at baseline were followed for up to 22 years. Blood levels of n3-PUFAs, including α-linolenic acid from plants and eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid from seafood, were measured at baseline, six years, and 13 years. Healthy ageing was defined as survival without major chronic diseases (cardiovascular disease, cancer, lung disease, and severe chronic kidney disease) as well as the absence of cognitive or physical dysfunction. Events were centrally adjudicated or determined from medical records and diagnostic tests.

Study answer and limitations A higher long term level of n3-PUFA biomarkers from seafood (the sum of eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid, as well as eicosapentaenoic acid and docosapentaenoic acid individually), but not docosahexaenoic acid from seafood or α-linolenic acid from plants, was associated with a higher likelihood of healthy ageing, with 18% (95% confidence interval 7% to 28%), 15% (6% to 23%), and 16% (6% to 25%) difference in risk per interquintile range, respectively. Although we adjusted for other major risk factors and evaluated objective blood levels of n3-PUFAs, this observational study cannot establish cause and effect.

What this study adds These findings support guidelines for increased dietary consumption of n3-PUFAs from seafood in older adults.

Funding, competing interests, and data sharing
See bmj.com for funding and competing interests.
No additional data are available.

Figure opposite: Hazard ratios (95% confidence intervals) of 2330 unhealthy ageing events per interquintile range (IQR) of omega 3 polyunsaturated fatty acids (n3-PUFAs) after 22 years of maximum follow-up among 2622 older adultsThe IQR is equivalent to the difference between the midpoint of the first and fifth quintiles, estimated to be 0.12%, 0.64%, 0.40%, 2.40%, and 2.90% for the n3-PUFAs, respectively

COMMENTARY Fresh evidence provides clues to healthier, not just longer, lives

Populations across the world are living longer.[1] Between 2015 and 2050, the proportion of the population worldwide, who are aged over 60 will nearly double from 12% to 22%.[2] Amid this rapid shift in the age distribution, increases in longevity bring opportunities but also challenges at both individual and societal levels. While recognising the great achievement of extended longevity, the evidence base for an improved healthspan (the length of time an individual is able to maintain good health)[3] is less encouraging, highlighting the need for research on healthy ageing.[4]

In a linked paper, Lai and colleagues investigate the association between circulating levels of omega 3 polyunsaturated fatty acids (n3-PUFAs) and healthy ageing in a large sample of older adults.[5]

Plasma phospholipid n3-PUFAs levels were measured at baseline and at six and 13 years, providing an objective assessment of four individual n3-PUFAs: two derived largely from seafood (eicosapentaenoic acid and docosahexaenoic acid), one predominantly. endogenous (docosapentaenoic acid), and one derived largely from plants (α-linolenic acid).

Through review of medical records and diagnostic tests, the authors determined that 89% of participants experienced unhealthy ageing during follow-up, while 11% experienced healthy ageing—defined as survival without major chronic diseases and without cognitive or physical dysfunction. After adjustment for covariates, weighted cumulative mean concentrations of eicosapentaenoic acid from seafood in the highest group were associated with a 24% lower risk of unhealthy ageing than concentrations in the lowest group. For the predominantly endogenously metabolised docosapentaenoic acid, the top three groups were associated with an 18% to 21% reduction in the risk of unhealthy ageing. Docosahexaenoic acid from seafood and α-linolenic acid from plants were not associated with healthy ageing.

Repeat measures

A rich body of literature suggests a protective role of n3-PUFAs in reducing cardiovascular risk,[6] whereas mixed or inconclusive findings have been reported for the other components of the unhealthy ageing examined in this study: cancer, lung disease, severe chronic kidney disease, and cognitive and physical dysfunction.[7-11] Self reported dietary data that are potentially subject to recall bias and measurement errors may partially contribute to these inconsistencies. Lai and colleagues make a valuable contribution, by combining reported dietary data with repeated measurements of biomarkers to account for trends over time in individual n3-PUFAs.

A few other points are worth considering when interpreting this study's findings. Firstly, biomarker concentrations are a function of both dietary intake and metabolism, influenced by the interplay of exogenous and genetic factors that are difficult to separate.

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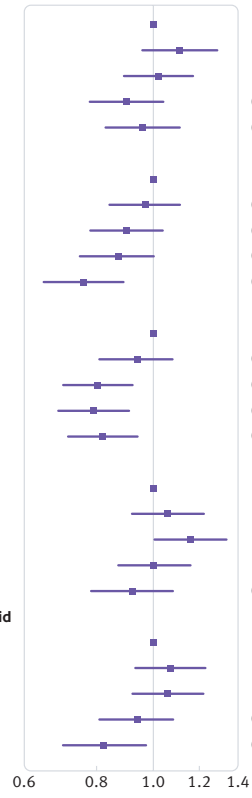
n3-PUFAs	No of events/total (per 1000 person years)	Median (% total fatty acids)	Hazard ratio (95% CI)	Hazard ratio (95% CI)	P value for trend
α-linolenic acid					
Group 1	334/369 (106)	0.09		1 (Reference)	
Group 2	421/457 (119)	0.11		1.11 (0.96 to 1.29)	
Group 3	523/583 (111)	0.14		1.02 (0.89 to 1.17)	0.006
Group 4	527/598 (100)	0.17		0.90 (0.78 to 1.04)	
Group 5	525/615 (102)	0.21		0.96 (0.83 to 1.11)	
Eicosapentaenoic acid					
Group 1	395/435 (117)	0.30		1 (Reference)	
Group 2	462/504 (115)	0.42		0.97 (0.84 to 1.11)	
Group 3	478/542 (109)	0.52		0.90 (0.78 to 1.04)	<0.001
Group 4	487/549 (103)	0.65		0.87 (0.75 to 1.00)	
Group 5	507/590 (97)	0.96		0.76 (0.65 to 0.89)	
Docosapentaenoic acid					
Group 1	388/423 (113)	0.64		1 (Reference)	
Group 2	391/425 (109)	0.75		0.94 (0.81 to 1.08)	
Group 3	438/502 (100)	0.82		0.80 (0.70 to 0.92)	0.003
Group 4	503/574 (104)	0.91		0.79 (0.69 to 0.91)	
Group 5	610/698 (109)	1.04		0.82 (0.71 to 0.94)	
Docosahexaenoic acid					
Group 1	375/427 (105)	1.96		1 (Reference)	
Group 2	465/511 (110)	2.44		1.06 (0.92 to 1.22)	
Group 3	485/536 (118)	2.89		1.16 (1.01 to 1.34)	0.119
Group 4	515/588 (105)	3.40		1.00 (0.87 to 1.16)	
Group 5	490/560 (99)	4.40		0.92 (0.78 to 1.08)	
Eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid					
Group 1	375/420 (108)	3.19		1 (Reference)	
Group 2	467/513 (112)	3.75		1.07 (0.93 to 1.23)	
Group 3	499/552 (121)	4.24		1.06 (0.92 to 1.22)	0.001
Group 4	476/554 (99)	4.85		0.94 (0.81 to 1.08)	
Group 5	513/583 (99)	6.15		0.82 (0.70 to 0.97)	



Secondly, associations between eicosapentaenoic acid and healthy ageing and between combined eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid and healthy ageing were only significant in the highest group. So who was in this top group, and could high n3-PUFA concentrations simply be a marker of some unmeasured confounding advantage through life? The study cohort was born in the 1910s and 1920s,[13] a generation characterised by long term improvements in population level socioeconomic resources,[14] which may influence longevity and health across the lifespan. Indeed, educational attainment was among the strongest covariates in this study. Therefore, we cannot rule out the possibility of differential exposures across the n3-PUFA quintiles to unmeasured chronic and acute stressors related to socioeconomic resources.

We caution against using these findings to inform public health policy or nutritional guidelines

Thirdly, the median concentrations of α-linolenic acid across groups accounted for just 0.09% to 0.21% of total fatty acids, approximately one third of eicosapentaenoic acid, one fifth of docosapentaenoic acid, and one twentieth of docosahexaenoic acid circulating concentrations. The limited variation in α-linolenic acid concentrations and vegetable intakes in this predominantly white study population may have contributed to the null association between α-linolenic acid derived from plants and healthy ageing. Further research is needed in populations with more diverse dietary patterns.

Epidemiological associations cannot infer causality, so we caution against using these findings to inform public health policy or nutritional guidelines. We live in challenging times, when lifespans are increasing but healthy lifespans are not. Following the World Health Organization's policy framework for healthy ageing,[15] any evidence based clues to improve health in later life are welcome, but additional efforts to accelerate this area of research are essential.

Cite this as: *BMJ* 2018;363:k4263

Find the full version with references at http://dx.doi.org/10.1136/bmj.k4263

ORIGINAL RESEARCH Nationwide cohort study

Pre-eclampsia and risk of dementia later in life

Basit S, Wohlfahrt J, Boyd HA

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Find this at: http://dx.doi.org/10.1136/bmj.k4109

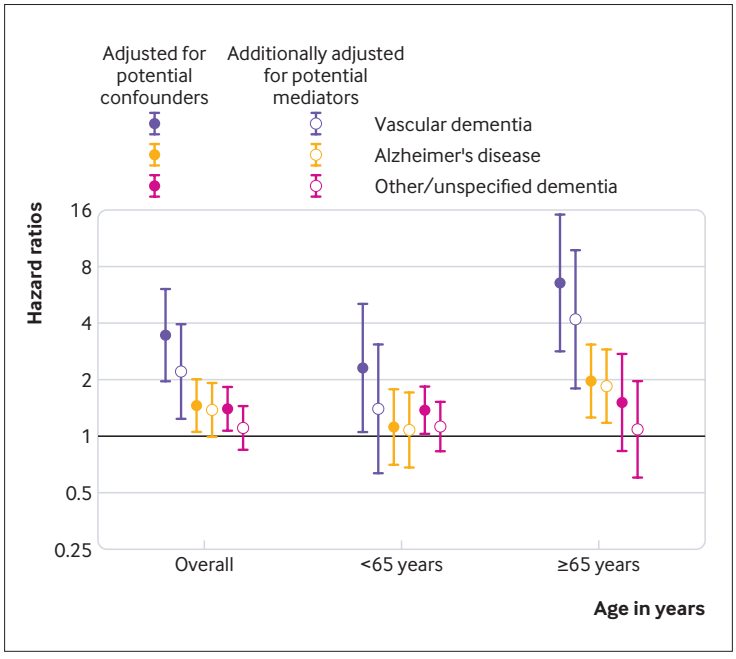
Study question Is pre-eclampsia associated with later dementia, overall and by dementia subtype and timing of onset?

Methods This register based cohort study of more than 1.1 million women with pregnancies in Denmark in 1978-2015 used Cox regression to compare the risks of dementia among women with and without a history of pre-eclampsia.

Study answer and limitations Women with a history of pre-eclampsia had more than three times the risk of vascular dementia later in life (hazard ratio 3.46, 95% confidence interval 1.97 to 6.10), compared with women with no history of pre-eclampsia. In contrast, pre-eclampsia was only modestly associated with the risk of Alzheimer's disease (hazard ratio 1.45, 1.05 to 1.99). The associations persisted after adjustment for comorbidities. Sensitivity analyses suggested that confounding by obesity was unlikely to explain the observed associations for vascular dementia, but the possibility of residual confounding by unmeasured confounders cannot be ruled out.

What this study adds This study indicates that pre-eclampsia is associated with an increased risk of later dementia, particularly vascular dementia, suggesting that pre-eclampsia and vascular dementia may share underlying mechanisms or susceptibility pathways.

Competing interests, funding, and data sharing SB was partially supported by a grant from the Danish Council for Independent Research. The study was based on Danish national register data, which can be obtained by submitting a research protocol to the Danish Data Protection Agency (Datatilsynet) and then, once permission has been received, applying to the Ministry of Health's Research Service (Forskerservice) at forskerservice@ssi.dk.



Associations between history of pre-eclampsia and dementia, overall, by dementia subtype, and by attained age, in cohort of women with ≥1 live birth or stillbirth in 1978-2015 in Denmark. Hazard ratios with 95% confidential intervals adjusted for birth year (5 year intervals), parity (1, 2, ≥3 live births and/or stillbirths), and region of most recent delivery (potential confounders); age was underlying time scale in Cox model. Potential mediators additionally adjusted for were cardiovascular disease, stroke, hypertension, chronic kidney disease, and diabetes

CORRECTION

In August, we issued a correction (*BMJ* 2018;362:k3210) to a 2016 research paper by Hemkens and colleagues (*BMJ* 2016;352:i493), in relation to their approach in comparing treatment effects on mortality.

The correction includes the authors' response and reanalysis of the original paper's data, which did not change the overall results or interpretation (hence our decision that a correction rather than a retraction was warranted).

Two additional linked articles (*BMJ* 2018;362:k3213; *BMJ* 2018;362:k3259) discuss how the correction came about, and the steps taken to resolve it.

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