research

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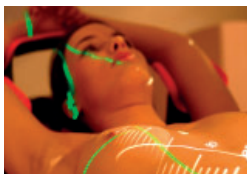

Targeted intraoperative radiotherapy for early breast cancer
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ORIGINAL RESEARCH National cohort and co-sibling study

Preterm delivery and long term mortality in women

Crump C, Sundquist J, Sundquist K

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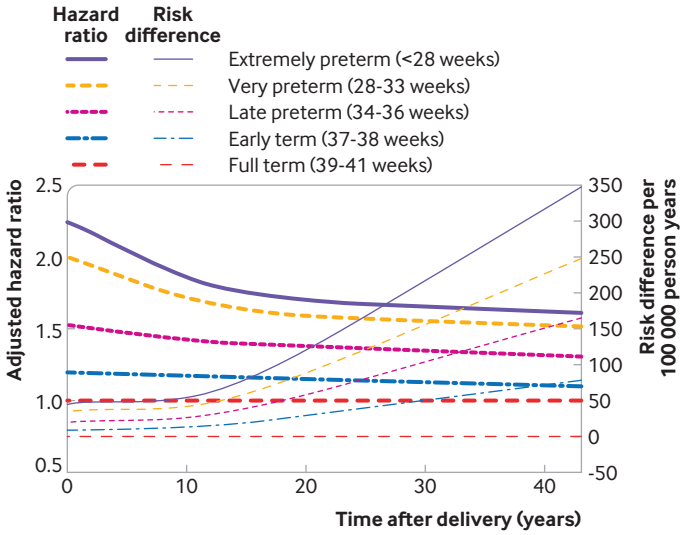
Study question Is preterm delivery associated with an increased risk of long term mortality in women?

Methods A national cohort study was conducted in all 2 189 477 women in Sweden who had a singleton delivery in 1973-2015. Length of pregnancy was examined in relation to all cause and cause specific mortality up to 2016. Cox regression was used to calculate hazard ratios while adjusting for confounders, and co-sibling analyses assessed the potential influence of unmeasured shared familial (genetic and environmental) factors.

Study answer and limitations A shorter length of pregnancy was associated with an increased risk of long term mortality, after adjusting for several factors. In the first 10 years after delivery, the adjusted hazard ratio for all cause mortality associated with preterm delivery (<37 weeks) was 1.73 (95% confidence interval 1.61 to 1.87), and when further stratified was 2.20 (1.63 to 2.96) for extremely preterm delivery (22-27 weeks), 2.28 (2.01 to 2.58) for very preterm delivery (28-33 weeks), 1.52 (1.39 to 1.67) for late preterm delivery (34-36 weeks), and 1.19 (1.12 to 1.27) for early term delivery (37-38 weeks) compared with full term delivery (39-41 weeks). These risks declined but remained significantly raised after longer follow-up times: for preterm versus full term births, 10-19 years after delivery, the adjusted hazard ratio was 1.45 (95% confidence interval 1.37 to 1.53); 20-44 years after delivery, the adjusted hazard ratio was 1.37 (1.33 to 1.41). These findings did not seem to be attributable to shared genetic or environmental factors within families. Several causes were identified, including cardiovascular and respiratory disorders, diabetes, and cancer. This study was limited to Sweden and the results might not be applicable to other countries.



Hazard ratios and absolute risk differences for all cause mortality in women by length of pregnancy compared with full term, Sweden, 1973-2016

What this study adds The findings suggested that preterm and early term delivery were independent risk factors for premature mortality in women up to 40 years later. Women who deliver prematurely might need long term follow-up for detection and treatment of chronic disorders associated with early mortality.

Funding, competing interests, and data sharing This study was supported by the National Heart, Lung, and Blood Institute at National Institutes of Health (R01HL139536); the Swedish Research Council; the Swedish Heart-Lung Foundation; and ALF project grant, Region Skåne/Lund University, Sweden.

The authors have no competing interests. No additional data are available.

Air pollution and family related determinants of asthma onset and persistent wheezing in children

Holst GJ, Pedersen CB, Thygesen M, et al

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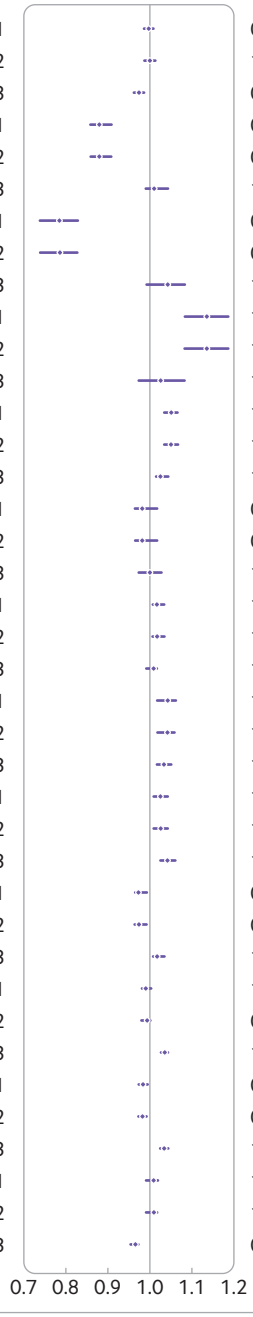
Study question What are the potential risk factors for onset of asthma and persistent wheezing in children?

Methods This registry based study followed Danish children born from 1997 to 2014 for onset of asthma and persistent wheezing from their 1st to 15th birthday. Hazard ratios were estimated using a time matched, case-control design. Information on asthma incidence, parental asthma, maternal smoking, air pollution, and parental education and income was derived from nationwide health registries linked with detailed modelled air pollution concentrations.

Study answer and limitations A higher incidence of asthma was found in children of parents with asthma (adjusted hazard ratio 2.29, 95% confidence interval 2.22 to 2.35) and mothers who smoked during pregnancy (1.20, 1.18 to 1.22), whereas a lower incidence was found in children of parents with high educational attainment (0.72, 0.69 to 0.75) and high incomes (0.85, 0.81 to 0.89). Exposure to particulate matter ≤2.5 µm ($PM_{2.5}$) and ≤10 µm (PM_{10}) and nitrogen dioxide was associated with an increased risk of asthma and persistent wheezing, with hazard ratios per 5 µg/m^3 increase in pollutant concentrations 1.05 (1.03 to 1.07) for $PM_{2.5}$, 1.04 (1.02 to 1.06) for PM_{10}, and 1.04 (1.03 to 1.04) for nitrogen dioxide. Only the positive association of $PM_{2.5}$ with asthma and persistent wheezing remained robust across the different models and in sensitivity analyses.

What this study adds The findings of this study suggest that children exposed to higher levels of $PM_{2.5}$ are more likely to develop asthma and persistent wheezing than children who are not exposed. Other risk factors associated with these outcomes were parental asthma, parental education, and maternal smoking during pregnancy.

Air pollutants	Increase	Model	Hazard ratio (95% CI)
Sea salt	1 µg/m^3	Model 1	0.99 (0.99 to 1.01)
		Model 2	1.00 (0.99 to 1.01)
		Model 3	0.97 (0.96 to 0.97)
Organic carbon	1 µg/m^3	Model 1	0.88 (0.86 to 0.91)
		Model 2	0.87 (0.85 to 0.90)
		Model 3	1.01 (0.99 to 1.05)
Elemental carbon	1 µg/m^3	Model 1	0.80 (0.76 to 0.84)
		Model 2	0.78 (0.74 to 0.82)
		Model 3	1.05 (0.99 to 1.10)
Ammonium	1 µg/m^3	Model 1	1.21 (1.14 to 1.28)
		Model 2	1.17 (1.10 to 1.24)
		Model 3	1.03 (0.97 to 1.10)
Nitrate	5 µg/m^3	Model 1	1.07 (1.05 to 1.09)
		Model 2	1.06 (1.04 to 1.08)
		Model 3	1.03 (1.02 to 1.05)
Sulfate	5 µg/m^3	Model 1	0.99 (0.96 to 1.03)
		Model 2	0.98 (0.96 to 1.02)
		Model 3	1.00 (0.97 to 1.03)
Secondary inorganic aerosols	5 µg/m^3	Model 1	1.03 (1.02 to 1.05)
		Model 2	1.02 (1.01 to 1.04)
		Model 3	1.01 (0.99 to 1.02)
PM_{10}	5 µg/m^3	Model 1	1.06 (1.03 to 1.08)
		Model 2	1.05 (1.02 to 1.07)
		Model 3	1.04 (1.02 to 1.06)
$PM_{2.5}$	5 µg/m^3	Model 1	1.04 (1.02 to 1.05)
		Model 2	1.03 (1.01 to 1.05)
		Model 3	1.05 (1.03 to 1.07)
Sulphur dioxide	5 µg/m^3	Model 1	0.98 (0.96 to 0.99)
		Model 2	0.97 (0.96 to 0.99)
		Model 3	1.02 (1.01 to 1.04)
Nitrogen oxide + nitrogen dioxide	10 µg/m^3	Model 1	1.00 (0.99 to 1.00)
		Model 2	0.99 (0.98 to 1.00)
		Model 3	1.04 (1.03 to 1.04)
Nitrogen dioxide	10 µg/m^3	Model 1	0.98 (0.97 to 0.99)
		Model 2	0.98 (0.97 to 0.99)
		Model 3	1.04 (1.03 to 1.04)
Ozone	10 µg/m^3	Model 1	1.01 (0.99 to 1.02)
		Model 2	1.01 (0.99 to 1.02)
		Model 3	0.96 (0.95 to 0.97)



Effects of air pollutants on risk of asthma and persistent wheezing. Model 1 was adjusted for sex, age, and calendar year. Model 2 was additionally adjusted for parental asthma. Model 3 was additionally adjusted for parental income and parental education

Funding, competing interests, and data sharing Funding was provided by NordForsk under the Nordic Programme on Health and Welfare (project No 75007): understanding the link between air pollution and distribution of related health impacts and welfare in the Nordic countries (NordicWelfAir), and by BERTHA—the Danish Big Data Centre for Environment and Health funded by a grant from the Novo Nordisk Foundation Challenge Programme (grant NNF17OC0027864). No other competing interests. No additional data are available.

Self-management interventions to reduce healthcare use and improve quality of life among patients with asthma

Hodkinson A, Bower P, Grigoroglou C, et al

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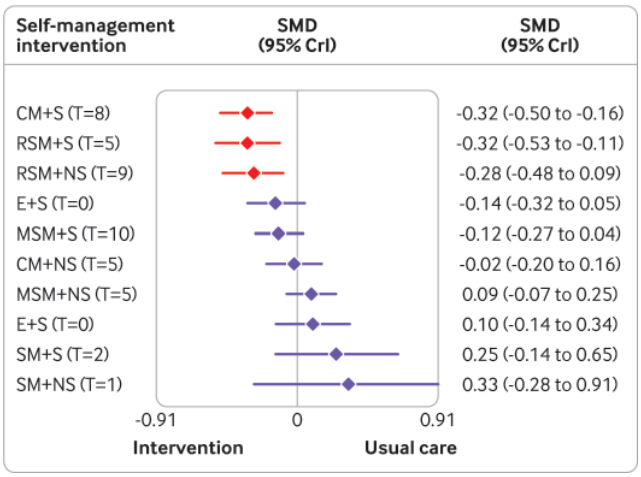
Study question How do the effects of different models of self-management intervention for managing asthma among adults and young people compare, and which models are best suited to widespread implementation?

Methods This systematic review and network meta-analysis included randomised controlled trials involving different self-management models for patients of all ages with asthma. Primary outcomes were healthcare use (hospital admission or emergency visit) and quality of life. Both were analysed with standardised mean differences (SMDs) and 95% credible intervals and were estimated using bayesian network meta-analysis with random effects. Heterogeneity, consistency and inconsistency, and publication bias were also assessed using GRADE.

Study answer and limitations Regularly supported self-management reduces the use of healthcare resources and improves quality of life across all levels of asthma severity. Although this investment in time for regularly supported self-management is offset by a reduction in unscheduled healthcare use, data on costs need to be more adequately reported and collected in future research to allow for a more comprehensive economic assessment.

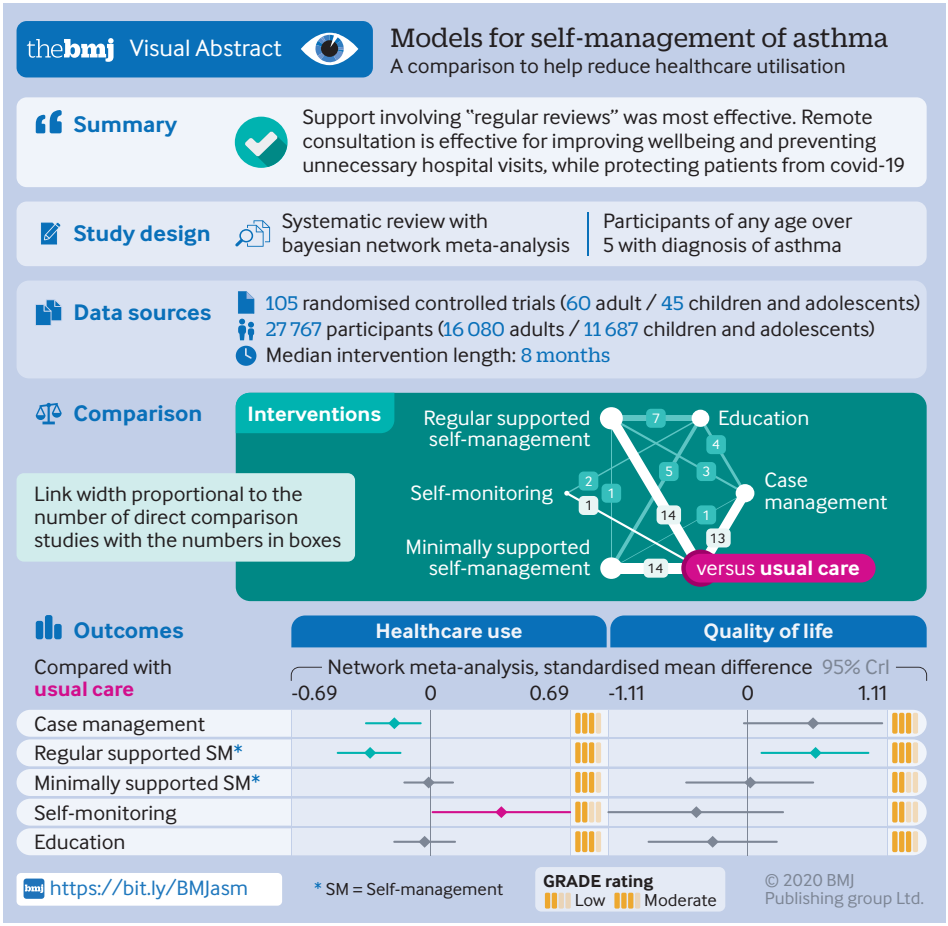
What this study adds This network meta-analysis included 105 trials comprising 27 767 participants that assessed four different levels of support for self-management of asthma (no support, minimal support, regular review, and case management). Support involving regular reviews totalling at least two hours was effective at establishing self-management skills and was significantly better than usual care at reducing healthcare use. Multidisciplinary case management should be reserved for patients with complex disease. Unsupported or minimally supported self-management programmes were not effective.



Forest plot of network meta-analysis of healthcare use after adjustment for severity of asthma at baseline. CrI=credible interval; CM=multidisciplinary case management; E=education; MSM=minimally supported self-management; NS=trials in patients with mild to moderate asthma; RSM=regularly supported self-management; S=trials in patients with severe asthma; SM=self-monitoring; SMD=standardised mean difference; T=number of studies providing direct evidence

Funding, competing interests, and data sharing This study is funded by the Evidence Synthesis Working Group (project 390), which is supported by the National Institute for Health Research School for Primary Care Research. No competing interests declared. Summary level data are available on request from the corresponding author, and the statistical code is provided in the appendix.

Study registration PROSPERO CRD42019121350.



Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer

Vaidya JS, Bulsara M, Baum M, et al

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Study question Can risk adapted targeted intraoperative radiotherapy (TARGIT-IORT) delivered as a single dose during lumpectomy effectively replace postoperative whole breast external beam radiotherapy (EBRT) for early breast cancer, and what are the long term outcomes?

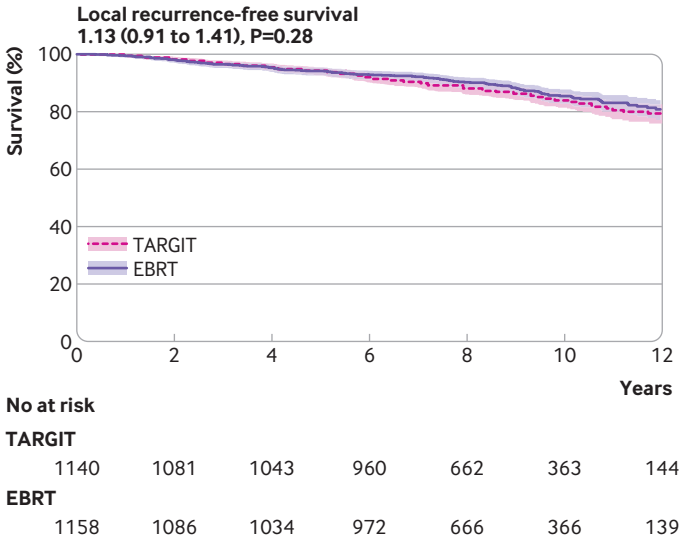
Methods The TARGIT-A international randomised controlled trial (32 centres in 10 countries in the United Kingdom, Europe, Australia, and North America) recruited 2298 women aged 45 years and older with invasive ductal carcinoma up to 3.5 cm (lymph node stage cN0-N1) who were eligible for breast conservation. Participants were randomised before lumpectomy to either single dose TARGIT-IORT or EBRT (standard daily fractionated course over three to six weeks). The main outcome measures were non-inferiority at a margin of 2.5% for five year local recurrence rate, and long term survival.

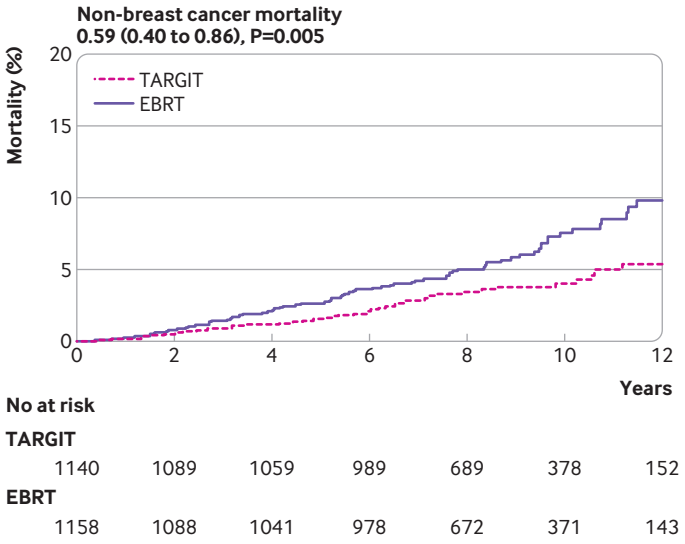
Study answer and limitations 1140 patients were randomised to TARGIT-IORT and 1158 to EBRT. The study found that TARGIT-IORT was non-inferior to EBRT for local recurrence. At five year complete follow-up the local recurrence risk was 2.11% (24/1140) for TARGIT-IORT compared with 0.95% (11/1158) for EBRT (difference 1.16%, 90% confidence interval 0.32% to 1.99%). 14 fewer deaths occurred with TARGIT-IORT than with EBRT (42/1140 *v* 56/1158). With long term follow-up (median 8.6 years) no statistically significant difference in any breast cancer outcome was found (such as local recurrence-free survival, mastectomy-free survival, and breast cancer mortality), and mortality from other causes was significantly lower in the TARGIT-IORT arm (45 *v* 74 deaths, hazard ratio 0.59, 95% confidence interval 0.40 to 0.86, P=0.005). Two major risk factors for cardiovascular disease and malignant disease were collected (age and body mass index), and they were well balanced between the two randomised arms of this large trial.

What this study adds For most patients with early breast cancer, immediate single dose TARGIT-IORT during lumpectomy was an effective alternative to EBRT, with comparable long term efficacy for cancer control and lower non-breast cancer mortality. TARGIT-IORT should be discussed with eligible patients when breast conserving surgery is planned.

Funding, competing interests, and data sharing Funding was provided by the United Kingdom National Institute for Health Research Health Technology Assessment programme, University College London (UCL) Comprehensive Biomedical Research Centre, and Cancer Research Campaign (now Cancer Research UK). Carl Zeiss sponsored travel for some authors. Data sharing as per UCL policy. Full details available on bmj.com.

Trial registration ISRCTN34086741, NCT00983684.





Long term outcomes of the randomised TARGIT-A trial comparing risk adapted targeted intraoperative radiotherapy (TARGIT) delivered as single dose during lumpectomy with postoperative whole breast external beam radiotherapy (EBRT) for early breast cancer. Data under titles are hazard ratios (95% confidence intervals) and log rank test P values