First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study

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EDITORIAL by Aiken and Smith

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News: Children's lifestyles pose "unacceptable" cardiovascular risk, warns charity (*BMJ* 2013;347:f5100)
Editorial: Maternal obesity and heart disease in the offspring (*BMJ* 2013;347:f4960)
Editorial: Fetal risk from ACE inhibitors in the first trimester (*BMJ* 2011;343:d6667)

STUDY QUESTION

Is variation in first trimester fetal growth associated with cardiovascular outcomes in school age children?

SUMMARY ANSWER

Impaired first trimester fetal growth is associated with an adverse cardiovascular risk profile in school age children.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Low birth weight is associated with cardiovascular disease in adulthood, but not much is known about the specific critical periods in fetal life or infancy. First trimester fetal development might be critical for cardiovascular health in later life.

Participants and setting

We studied mothers and their children with a first trimester fetal crown to rump length measurement, a reliable first day of their last menstrual period, and a regular menstrual cycle, living in the city of Rotterdam, the Netherlands.

Design, size, and duration

The study was nested in a population based prospective cohort study. In total, 1184 children whose mothers had a reliable first day of their last menstrual period and a regular cycle and who had a first trimester fetal crown to rump length measurement (10-14 weeks of gestation) participated in detailed cardiovascular follow-up studies at the age of 6 years. Cardiovascular outcomes of interest included body mass index, body fat distribution, blood pressure, lipid concentrations, and insulin measures, which are known risk factors for cardiovascular disease in adulthood and track from childhood to adulthood.

First trimester fetal growth and childhood cardiovascular risk factors

Risk factor	Difference (95% CI) in cardiovascular risk factors per SDS change in first trimester fetal crown to rump length*
Body mass index (kg/m^2)	−0.04 (−0.14 to 0.05)
Total fat mass (%)	−0.30 (−0.57 to −0.03)
Android/gynoid fat mass ratio (%)	−0.53 (−0.89 to −0.17)
Systolic blood pressure (mm Hg)	−0.10 (−0.59 to 0.39)
Diastolic blood pressure (mm Hg)	−0.43 (−0.84 to -0.01)
Total cholesterol (mmol/L)	−0.05 (−0.10 to 0.00)
HDL cholesterol (mmol/L)	−0.01 (−0.04 to 0.01)
LDL cholesterol (mmol/L)	−0.04 (−0.09 to 0.00)

HDL=high density lipoprotein; LDL=low density lipoprotein; SDS=standard deviation score.
*Values are regression coefficients (95% confidence interval) adjusted for confounders.

Main results and the role of chance

A greater first trimester fetal crown to rump length was associated with a lower total fat mass, android fat mass, android/gynoid fat mass ratio, diastolic blood pressure, total cholesterol, and low density lipoprotein cholesterol. First trimester fetal growth was not associated with other cardiovascular outcomes. A greater first trimester fetal crown to rump length was also associated with a lower risk of clustering of cardiovascular risk factors in childhood. Longitudinal growth analyses showed that compared with school age children without clustering of cardiovascular risk factors, those with clustering had a smaller first trimester fetal crown to rump length and lower second and third trimester estimated fetal weight but higher weight growth from the age of 6 months onwards.

Bias, confounding, and other reasons for caution

Reliable information and first trimester fetal growth assessment were available in only a subgroup of the full large scale population based cohort study. The population for analysis was a relatively healthy and highly educated population. Selection of the study sample might have affected the generalisability of the results. Although we observed that stepwise adjustment for various different potential maternal and childhood confounders did not strongly change the effect estimates, residual confounding may still be a problem, as in any observational study.

Generalisability to other populations

Whether the observed associations are similar in high risk populations should be studied further.

Study funding/potential competing interests

VWVJ received funding from the Netherlands Organization of Scientific Research, Netherlands Organization of Health Research and Development. OHF works in ErasmusAGE, a centre for ageing research across the life course funded by Nestle Nutrition, Metagenics, and AXA. RG received funding from the European Union's Seventh Framework Programme, project EarlyNutrition.

Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial

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EDITORIAL by Kalager and colleagues

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STUDY QUESTION

To what extent does mammography screening reduce mortality from breast cancer?

SUMMARY ANSWER

Annual mammography in women aged 40-59 does not reduce mortality from breast cancer beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Women with non-palpable breast cancer detected by mammography experience long term survival that is superior to that of women with palpable breast cancer. This trial found that annual mammography screening detected a significant number of small non-palpable breast cancers but had no impact on breast cancer mortality.

Design

Women aged 40-59 were randomly assigned to a mammography arm (five annual mammography screens) or control arm (no mammography). Women aged 40-49 in the mammography arm and all women aged 50-59 in both arms received five annual physical breast examinations, and women aged 40-49 in the control arm received a single physical examination followed by usual care in the community. The women were followed for up to 25 years for incidence of breast cancer and breast cancer related deaths.

Participants and setting

89 835 women were randomised from 1980 to 1985. The study was conducted in 15 screening centres (located in teaching hospitals or cancer centres) in six Canadian provinces. The central coordinating centre was at the University of Toronto.

Primary outcome

Mortality from breast cancer five years after screening and at six and seven years (when we assumed different lengths of screening periods), and at the completion of follow-up at 25 years.

Deaths from breast cancer to 31 December 2005, by study arm and year of diagnosis

Study year	Mammography arm (n=44 925)	Control arm (n=44 910)
Deaths from breast cancers detected in years 1-5	180	171
Breast cancer deaths per 10 000 women	40.1	38.1
Deaths from breast cancers detected in years 6-25	298	321
Breast cancer deaths per 10 000 women	66.3	71.4
Total deaths from breast cancers all years*	500	505
Breast cancer deaths per 10 000 women	108.4	110.2

*Year of diagnosis was not available for 35 additional women, 22 in mammography arm and 13 in control arm.

Main results and the role of chance

During the five year screening period, 666 invasive breast cancers were diagnosed in the mammography arm and 524 in the controls. 180 women in the mammography arm and 171 women in the control arm died of breast cancer. The overall hazard ratio for death from breast cancer diagnosed during the screening period associated with mammography was 1.05 (95% confidence interval 0.85 to 1.30). The findings for women aged 40-49 and 50-59 were almost identical. The cumulative mortality from all breast cancers diagnosed during the entire study period was similar between women in the mammography and control arms (hazard ratio 0.99, 95% confidence interval 0.88 to 1.12).

Harms

After 15 years of follow-up an excess of 106 cancers was observed in the mammography arm, attributable to over-diagnosis. This excess represents 22% of all screen detected invasive cancers, half of those detected by mammography alone. Therefore for every 424 women screened by mammography in the trial one breast cancer was over-diagnosed.

Bias, confounding, and other reasons for caution

The lack of an impact of mammography screening on mortality from breast cancer in this study cannot be explained by bias or confounding, lack of statistical power, or poor quality mammography. The risk of breast cancer was identical in the compared groups: after the screening period ended, breast cancer was diagnosed in 5.8% of women in the mammography arm and 5.9% of women in the control arm (P=0.80).

Generalisability to other populations

Early detection could be of greater benefit in communities where most cancers that present clinically are large and a high proportion node positive. In technically advanced countries, however, the rationale for screening by mammography should be urgently reassessed.

Study funding/potential competing interests

This study was supported by the Canadian Breast Cancer Research Alliance, Canadian Breast Cancer Research Initiative, Canadian Cancer Society, Health and Welfare Canada, National Cancer Institute of Canada, the Alberta Heritage Fund for Cancer Research, Manitoba Health Services Commission, Medical Research Council of Canada, le Ministère de la Sante´ et des Services Soçiaux du Québec, Nova Scotia Department of Health, and Ontario Ministry of Health.

Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis

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STUDY QUESTION

Is there a difference in long term survival rates of women with BRCA associated breast cancer who did and did not undergo a contralateral (bilateral) mastectomy?

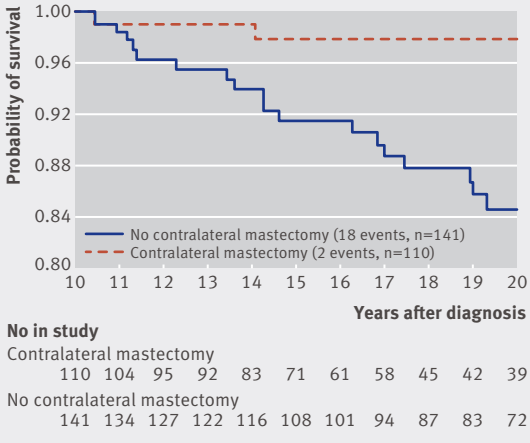
SUMMARY ANSWER

Women who are positive for the BRCA mutation and treated for stage I or II breast cancer with bilateral mastectomy are less likely to die from breast cancer than women who are treated with unilateral mastectomy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

In previous research of patients with BRCA associated breast cancer, mastectomy (versus lumpectomy) and contralateral mastectomy (versus unilateral mastectomy) were associated with large and statistically significant reductions in the risks of ipsilateral and contralateral breast cancer, respectively. We found that women with BRCA associated breast cancer treated with bilateral mastectomy were 48% less likely to die of breast cancer within 20 years than women treated with unilateral mastectomy. Therefore of 100 women treated with contralateral mastectomy, 87 will be alive at 20 years compared with 66 of 100 women treated with unilateral mastectomy.

Survival from 10 to 20 years after breast cancer, by contralateral mastectomy



Participants and setting

390 women from 12 participating North American clinical genetics centres with stage I or II breast cancer and a BRCA1 or BRCA2 mutation who were initially treated with unilateral or bilateral mastectomy.

Design, size, and duration

This longitudinal cohort study assessed survival in women with BRCA associated breast cancer treated with unilateral or bilateral mastectomy. Participants were identified through review of family histories of individuals seen in cancer genetics clinics. Medical records were reviewed for clinical presentation, medical and surgical treatments, and outcome. Patients were followed for up to 20 years from diagnosis.

Main results and the role of chance

79 women died of breast cancer in the follow-up period (18 in the bilateral mastectomy group and 61 in the unilateral mastectomy group). The median follow-up time was 14.3 years (range 10.1-20.0 years). At 20 years, the survival rate was 88% for women who had mastectomy of the contralateral breast and 66% for women who did not. In a multivariable analysis, controlling for age at diagnosis, year of diagnosis, treatment, and other prognostic features, contralateral mastectomy was associated with a 48% reduction in death from breast cancer (hazard ratio 0.52, 95% confidence interval 0.29 to 0.93; P=0.03).

Bias, confounding, and other reasons for caution

The choice of surgical treatment for breast cancer was not randomised and baseline imbalances in the treatment groups were present for several prognostic indicators. Therefore, in the survival analysis we adjusted for BRCA mutation, tumour size, nodal status, and treatment factors.

Generalisability to other populations

These findings are for women with BRCA associated breast cancer and cannot be generalised to women with sporadic breast cancer.

Study funding/potential competing interests

This study was funded by the Canadian Breast Cancer Foundation (Ontario Chapter).

Withdrawing performance indicators: retrospective analysis of general practice performance under UK Quality and Outcomes Framework

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- Editorial: What happens when pay for performance stops? (*BMJ* 2014;348:g1413
- Research: Exempting dissenting patients from pay for performance schemes: retrospective analysis of exception reporting in the UK Quality and Outcomes Framework (*BMJ* 2012;344:e2405)
- Research: Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK Quality and Outcomes Framework (*BMJ* 2011;342:d3590)
- Analysis: How to identify when a performance indicator has run its course (*BMJ* 2010;340:c1717)

STUDY QUESTION

What is the effect of withdrawing incentives on recorded quality of care, in the context of the UK Quality and Outcomes Framework pay for performance scheme introduced in April 2004?

SUMMARY ANSWER

Mean levels of performance were generally stable after removal of the incentives, in both the short term (for indicators removed in April 2011) and the long term (for indicators removed in April 2006).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The Quality and Outcomes Framework is a pay for performance programme under which increases in performance and a closing of the inequality gap have been observed. The (partial) removal of incentives seems to have had a very small effect on quality of care, indicating that replacing existing indicators with little potential for further improvement could provide an opportunity to maximise health benefits from the incentive scheme.

Participants and setting

We included data for 644 general practices, from 2004-05 to 2011-12, extracted from the Clinical Practice Research Datalink. We used data for all patients registered with any of the practices over the study period—13 772 992 in total.

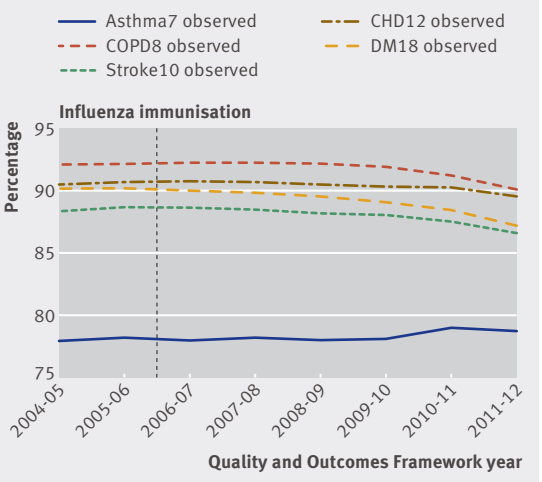
Design, size, and duration

We modelled performance on eight clinical quality indicators withdrawn from a national incentive scheme: influenza immunisation (asthma) and lithium treatment monitoring (psychosis), removed in April 2006; blood pressure monitoring (coronary heart disease, diabetes, stroke), cholesterol concentration monitoring (coronary heart disease, diabetes), and blood glucose monitoring (diabetes), removed in April 2011. We used multilevel mixed effects multiple linear regression models to quantify the effect of withdrawal of incentives in an interrupted time series analysis design.

Main results and the role of chance

Mean levels of performance were generally stable after the removal of the incentives, in both the short and long term. For the two indicators removed in April 2006, levels in 2011-12 were very close to 2005-06 levels, although a small but statistically significant drop was estimated for influenza immunisation. For five of the six indicators withdrawn in April 2011, we observed no significant effect on performance after removal and differences between predicted and observed scores were small. Performance on related outcome indicators retained in the scheme (such as blood pressure control) was generally unaffected.

Trends for removed Asthma7 indicator and related unremoved indicators of influenza immunisation



Vertical line indicates timing of Asthma7 removal

Bias, confounding, and other reasons for caution

The withdrawn monitoring indicators we modelled remained incentivised through their linked outcome indicators that remained in the scheme, so a strong indirect incentive for taking these measures still exists. Greater effects on performance may be apparent for withdrawn measurement indicators without a linked incentivised outcome. In addition, indirect incentivisation for influenza immunisation exists for certain subgroups of patients with asthma (aged 65 or over or with a comorbid condition under which an incentive exists). However, more than two thirds of those we examined did not have influenza immunization indirectly incentivised in any way.

Generalisability to other populations

Practices in the Clinical Practice Research Datalink are broadly representative in terms of local area deprivation, but they tend to be larger than the average English practice and use a single clinical computing system. We did sensitivity analyses to control for practice size, area deprivation, and changes in practices' characteristics over time, and our findings were similar. However, clinical system is a predictor of Quality and Outcomes Framework performance, and the generalisability of findings to all practices might be limited.

Study funding/potential competing interests

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