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Early fetal growth and risk factors for cardiovascular disease

Let's start at the very beginning, or even earlier

Catherine E M Aiken academic clinical fellow

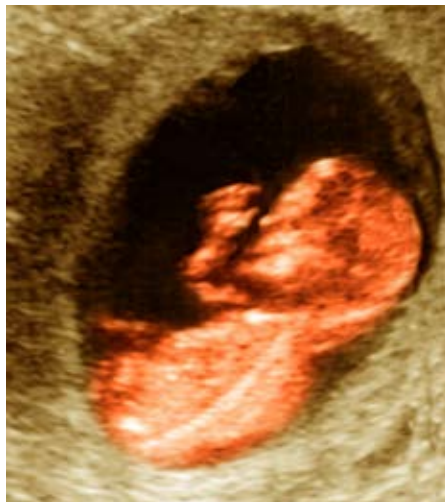
Gordon C S Smith professor, Department of Obstetrics and Gynaecology, University of Cambridge, Box 223, Rosie Hospital and NIHR Cambridge Comprehensive Biomedical Research Centre, Cambridge CB2 0SW, UK
gc52@cam.ac.uk

Some readers' principal response to the paper by Jaddoe and colleagues may be bemusement.¹ Why would anyone link growth of the fetus in the first trimester to risk factors for the cardiovascular killers of middle age? However, the rationale for the study is based around two large bodies of work that have concluded that fetal growth restriction is associated with an increased risk of cardiovascular—and many other—diseases in later life,² and also that fetal growth is profoundly influenced by conditions in the first trimester of pregnancy.³ Jaddoe and colleagues report new associations between apparently poor growth in the first trimester and a range of cardiovascular risk factors measured in school age children. Are the associations likely to be real? What mechanisms might be operating if they are? Lastly, what should we be doing about it?

Many aspects of this carefully conducted prospective cohort study support the validity of the conclusions. However, as the authors acknowledge, the possibility remains that some of their significant associations may have arisen by chance. False positive findings, or type 1 statistical errors, are always a risk in studies with many different outcomes and a large number of statistical tests. The many potential classifications of both outcomes and exposures are a further complication. Furthermore, the new study is one of many arising from the same cohort,⁴ and we know that repeated hypothesis testing increases the risk of type 1 errors still further. Although assembling such a feast of data but then denying oneself any more than a single morsel of analysis would be perverse, the conclusions of this study should be treated as hypothesis generating. The pre-existing body of work, however, suggests that Jaddoe and colleagues' findings are not data driven and will be reproducible.

Developmental programming hypothesis

Mechanisms that may explain the link between fetal growth and later cardiovascular risk factors have been explored extensively over the



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An extensive body of work now exists that supports the view that delivery of a small baby is a marker of maternal cardiovascular dysfunction

past 30 years, in both human cohorts and animal models.⁵ The idea that subtle influences on physiological systems occur early in development and are later magnified by the effects of growth and ageing to produce pathological phenotypes is well established. Studies have identified putative mechanisms—specifically, altered DNA methylation, mitochondrial DNA instability, and increased exposure to oxidative stress.^{6,7} Such mechanisms are likely to explain the trans-generational effects of certain environmental challenges in human populations.⁸

However, despite the plausibility and attractiveness of the developmental programming hypothesis in interpreting the results of Jaddoe and colleagues' study, consideration must be given to other explanations for a smaller than expected fetus in early pregnancy. A fetus may measure small for dates if ovulation occurred later than usual in the menstrual cycle. Hence, a smaller than expected fetus could be a marker for reproductive disorders in the mother, such as polycystic ovary syndrome, which predisposes women to prolonged menstrual cycles. Given that polycystic ovary syndrome is associated with the metabolic syndrome, and is also likely to have an important genetic element,⁹ a small fetus or baby may be a marker of maternal

genetic characteristics that might be inherited by the baby and lead to the associations described in the paper. Although Jaddoe and colleagues corrected estimates of fetal size for cycle length, the subtle effects of dating discrepancies are a problem with many such studies.

Consistent with the idea that reproductive dysfunction and cardiovascular disease could have a common genetic predisposition, we know that the birth weight of the infant is also inversely associated with the risk of cardiovascular disease in the mother and in the mother's parents.^{10,11} An extensive body of work now exists that supports the view that delivery of a small baby is a marker of maternal cardiovascular dysfunction.¹² Disentangling the effects on the fetus of maternal environmental stresses from the effects of maternal genetic and epigenetic predisposition to disease will be a major challenge for future studies.

For doctors, the pertinent question is whether these early effects can be modified. Can we identify interventions that might improve the early life environment and promote "normal" growth trajectories? On the basis of the current analysis, these interventions might be needed in the first trimester of pregnancy, during embryogenesis. Given the potential for interventions to cause serious harm at this stage of pregnancy, compelling evidence of safety will be needed before their evaluation. Hence, the appropriate response in the short term is that we need a deeper understanding of the strength, nature, and mechanisms of the reported associations before rushing to intervene.

Studies such as those of Jaddoe and colleagues and previous work suggest that researchers need to recruit cohorts of women in the very earliest stages of pregnancy or, ideally, before conception to ensure that the initiating events are captured.^{1,3} For future analyses of the determinants of the health of our children and the adults that they become, a key message may lie in the words written by Oscar Hammerstein II and immortalised by Julie Andrews: "Let's start at the very beginning, a very good place to start."

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Too much mammography

Long term follow-up does not support screening women under 60

Mette Kalager medical doctor and researcher, Department of Health Management and Health Economics, University of Oslo, Oslo, Norway; Department of Epidemiology, Harvard School of Public Health, Boston, MA, US; Department of Research and Development, Telemark Hospital, Skien, Norway mette.kalager@medisin.uio.no

Hans-Olov Adami professor, Department of Health Management and Health Economics, University of Oslo, Oslo, Norway; Department of Epidemiology, Harvard School of Public Health, Boston, MA, US; Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Michael Bretthauer professor, Department of Health Management and Health Economics, University of Oslo, Oslo, Norway; Department of Epidemiology, Harvard School of Public Health, Boston, MA, US; Department of Transplantation Medicine, Oslo University Hospital, Oslo, Norway; Department of Medicine, Sørlandet Hospital Kristiansand, Kristiansand, Norway

Before widely implemented, mammography screening was tested in randomised controlled trials in the 1960s to 80s. Meta-analyses of these trials showed a relative reduction in deaths from breast cancer of between 15% and 25% among women aged 50 to 69.¹⁻³ Only the Canadian National Breast Screening Study showed no reduction in breast cancer mortality.¹⁻³ This large randomised controlled trial compared physical breast examination with combined physical breast examination and annual mammography in women aged 40 to 59.¹⁻³

In a linked paper, Miller and colleagues present the results for up to 25 years of follow-up in the Canadian study.⁴ No difference in breast cancer mortality was observed between the mammography and control arms, whereas a significant excess incidence of invasive breast cancer was observed in the mammography arm, resulting in 22% overdiagnosis. This means that 22% of screen detected invasive cancers would not have reduced a woman's life expectancy if left undetected.

The major strengths of this study include its randomised design, intense intervention with five annual mammography screenings, high compliance, and complete, long term follow-up. The lack of mortality benefit is also biologically plausible because the mean tumour size was 19 mm in the screening group and 21 mm in the control group. This 2 mm difference—which might be even smaller if overdiagnosed cancers could be excluded from the screening group—represents a minimal proportion of the entire clinical course for breast tumours.

But the trial also has some potential limitations. No quantitative data are available on the degree

Because the scientific rationale to recommend screening or not does not differ noticeably between breast and prostate cancer, political pressure and beliefs might have a role

of contamination in the control arm or possible confounding by screening mammography after the trial. It seems unlikely, however, that such potential limitations would conceal a clinically important benefit. The rate of overdiagnosis did not include ductal carcinoma in situ, and the trial provides no data for women older than 60.

The Canadian study, launched in 1980, is the only trial to enroll participants in the modern era of routine adjuvant systemic treatment for breast cancer, and the women were educated in physical breast examination as advocated today.⁴ These important features may make this study more informative for a modern setting, compared with other randomised trials. The results of the study are strikingly similar—for both lack of efficacy and extent of overdiagnosis—to studies evaluating today's screening programmes.⁵⁻⁷ The amount of overdiagnosis in current screening programmes might be even higher than that reported in the Canadian study,⁴ because ductal carcinoma in situ, which accounts for 1 in 4 breast cancers detected in screening programmes,⁸ was not included in the analyses.

Other studies also indicate that improved treatment rather than screening is the reason for the recent decline in breast cancer mortality.⁵⁻⁷ Even though different studies arrive at different reductions in breast cancer mortality (from 10% to 25%), these benefits translate to only marginal differences in absolute effects. Much larger variation is seen in the estimates of overdiagnosis.⁶ In studies based on statistical modelling, overdiagnosis was less than 5%.⁶ In contrast, most observational studies report higher estimates of overdiagnosis, ranging from 22-54%,⁶ depending on denominator.⁹ When the number of breast cancers detected at screening is used as the denominator (as in the Canadian study), the amount of overdiagnosis observed in the previous randomised controlled trials is strikingly similar (22-24%).⁴⁻¹⁰

How does the data on mammography screening compare with that of prostate cancer screening by prostate specific antigen, which is currently

not encouraged in the United Kingdom and other countries owing to its small effect on mortality and large risk of overdiagnosis (www.screening.nhs.uk/prostatecancer)? The figure on bmj.com shows that the absolute harms (overdiagnosis) and benefits (mortality reduction) are not very different between the screening types. The 20 year risk of breast cancer for a 50 year old woman is 6.1% with screening (including 22% overdiagnosis⁴),¹¹ and 5.0% without screening; and the corresponding numbers for prostate cancer in a 50 year old man are 3.9% with screening (including 45% overdiagnosis¹²) and 2.7% without screening.¹¹ The 20 year risk of death from cancer for a 55 year old woman is 1.5% with screening (assuming a 20% reduction in mortality²)¹¹ and 1.9% without screening; and the corresponding numbers for prostate cancer in a 55 year old man are 1.0% with (assuming a 20% reduction in mortality¹²) and 1.3% without screening.¹¹

Nevertheless, the UK National Screening Committee does recommend mammography screening for breast cancer but not prostate specific antigen screening for prostate cancer, stating that the “aim is to only implement programs that do more good than harm and that the informed choice is a guided principle of screening” (www.screening.nhs.uk/screening). Because the scientific rationale to recommend screening or not does not differ noticeably between breast and prostate cancer, political pressure and beliefs might have a role.

Think it possible you may be mistaken

We agree with Miller and colleagues that “the rationale for screening by mammography be urgently reassessed by policy makers.” As time goes by we do indeed need more efficient mechanisms to reconsider priorities and recommendations for mammography screening and other medical interventions. This is not an easy task, because governments, research funders, scientists, and medical practitioners may have vested interests in continuing activities that are well established.

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Mutation carriers are about four to five times more likely than women without these mutations to develop cancer in the contralateral breast

Contralateral mastectomy for women with hereditary breast cancer

Still a very personal decision

Karin B Michels associate professor, Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA kmichels@research.bwh.harvard.edu

Angelina Jolie's disclosure in May 2013 of her prophylactic bilateral mastectomy triggered a wide range of reactions among women, caregivers, and scientists. In an editorial in the *New York Times* the actress announced that she was a carrier of a BRCA1 genetic mutation, significantly increasing her risk of breast and ovarian cancer. Jolie's decision was intended to lower her risk of developing and dying from breast cancer.

Carriers of a mutation in the BRCA1/2 gene who develop breast cancer face a decision similar to that of Jolie's: should they part with their unaffected breast to prevent a second tumour? The question such women ask is: will this reduce my risk of dying from breast cancer? In a linked paper, Metcalfe and colleagues present new data for consideration by affected women and their doctors. Results from this observational study suggest that preventive mastectomy of the contralateral breast may reduce the risk of dying from breast cancer by 48% within 20 years after the first diagnosis.

The prospect that 12% of women will develop breast cancer throughout their lifetime has raised awareness of the importance of the disease and has spurred research aiming at prevention and cure. The cumulative incidence of breast cancer is even higher among carriers of BRCA1/2 mutations: women with a mutation in this tumour suppressor gene have an approximately 60% risk of developing the disease during their lives. Moreover, among women with a genetic defect in BRCA1 or BRCA2, many breast cancers become apparent at an early age and often are the more aggressive types, such as triple negative breast cancer, and are therefore more lethal.

Interestingly, comparative data on the survival advantage of preventive contralateral mastectomy among BRCA1/2 carriers with breast cancer are limited. Metcalfe and colleagues derived their

study population from families with a documented BRCA mutation, and included women from these families with a diagnosis of early stage breast cancer before the age of 65. All 390 women included underwent mastectomy: 209 unilateral and 181 bilateral, with prophylactic mastectomy of the contralateral breast at initial surgery or during the following years. In this study, the apparent survival advantage among women with bilateral mastectomy was greatest during the second decade after diagnosis, although most deaths from breast cancer were noted during the first decade: 59 breast cancer related deaths occurred during the first 10 years and 20 (including nine among women with contralateral breast cancer) during the subsequent 10 years.

As with previous studies, the study by Metcalfe and colleagues is limited by the relatively small number of endpoints, which provide unstable estimates and make statistical inferences more challenging. The reduction in breast cancer

related deaths associated with bilateral mastectomy was statistically significant only during the second decade after initial diagnosis of breast cancer but not during the first decade. Moreover, sensitivity analyses confined to women for whom positive BRCA1/2 test results were available resulted in an effect estimate of similar magnitude but lacked statistical power to achieve significance. Subgroup analyses matched by propensity score had similar limitations, and generated a non-significant association

between bilateral mastectomy and a lower risk of breast cancer related death.

Randomised studies not feasible

Observational studies are further limited by the potential for confounding. Bilateral oophorectomy is an important factor potentially confounding the association between mastectomy and survival. In Metcalfe and colleagues' study, women who opted for bilateral mastectomy were 50% more likely to also undergo oophorectomy than women who underwent unilateral mastec-

tomy. Although this difference was adjusted for in the analyses, residual and unmeasured confounding by this and other factors may remain. In another recent study, contralateral mastectomy improved survival in women with BRCA1/2 associated breast cancer, but the 10 year survival of women who chose to also undergo oophorectomy was even higher. The least biased and hence most informative data for women making these decisions would come from randomised clinical trials. But randomisation of prophylactic contralateral mastectomy may not be feasible, given the personal and individual nature of the choice to remove a healthy breast surgically.

Carriers of BRCA1/2 mutations have an about five times increased lifetime risk of breast cancer in either breast. The risk of contralateral breast cancer is increased both for carriers of the mutation and for women with sporadic breast cancer, since first and second cancers are not independent events, but mutation carriers are about four to five times more likely than women without these mutations to develop cancer in the contralateral breast. Given the worse prognosis of BRCA1/2 associated breast cancers, the absence of mammary tissue after a contralateral mastectomy should translate into a reduction of breast cancer related deaths. Nevertheless, larger studies tackling this issue are needed and will undoubtedly be generated in the years to come.

But statistics remain statistics. Breasts are, however, not statistics. They are essential parts of women's identity, sexuality, and self perception. Parting with a breast may result in anxiety, lack of self esteem, and possibly depression. Parting with a healthy breast (or two) to prevent a probability is even more difficult. The decision to undergo a bilateral mastectomy is an individual and personal choice that a woman has to make together with her doctor. A woman needs to weigh up alternative options, including regular close monitoring and the use of tamoxifen or raloxifene, while considering the opportunities but also possible complications of reconstructive surgery. No statistics and no statistician can make this decision for her. Competing interests: None declared. Provenance and peer review: Commissioned; not externally peer reviewed.

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A tough decision, but her own

What obligations might doctors and society as a whole have to people who happen, for whatever reason, to find themselves in the UK and in need of healthcare?

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Overseas visitors and free NHS care

Doctors are providers of healthcare, not immigration officers

Julian Sheather deputy head of ethics, Ethics Department, BMA, London WC1H 9JP, UK JSheather@bma.org.uk
Martin Davies senior ethics adviser, Ethics Department, BMA, London WC1H 9JP, UK

In December 2013, the Department of Health published its latest plans to reform access to the NHS by overseas visitors in England.¹ Together with the introduction of a health surcharge for temporary migrants from the non-European Economic Area (EEA), access to NHS treatment by visitors, working migrants, and undocumented migrants is set to change.

Several drivers are at work—the current system is seen as too complex, too inefficient, and far too easily abused. There are high profile accusations that migrants set out systematically to defraud the NHS.² The changes are also taking place in an atmosphere of heightened anxiety around immigration. Attitudes are hardening, with calls for ever tighter immigration controls growing louder.

Decisions about entitlement to public goods and services are political and, therefore, ultimately a matter for parliament. The question of what obligations a wealthy state owes to non-citizens, both within and outside its borders, is a challenging and urgent moral one, but not one primarily for health professionals to answer. A raft of practical and administrative problems will need to be dealt with long before the changes take place. But doctors are nevertheless under an ordinary professional obligation to provide healthcare on the basis of need. So what is the nature of the statutory changes and what are their implications for professional ethics?

Under the current system, people are entitled to free NHS treatment if they are “ordinarily resident” in the United Kingdom or eligible under one of the exemptions in the current regulations. Specific services, such as treatment for communicable diseases, are also exempt from charge irrespective of residency status. The regulations in England currently allow charges to be raised only for NHS treatment provided in hospital.

Among the more important changes announced by the Department of Health is the extension of charging to primary care. Recognising that economic barriers to accessing a general practitioner could prevent control of communicable diseases and the early identification and management of conditions, with the economic



Spot the difference

and individual health implications this entails, GP consultations will remain free. The Department of Health is, however, considering charging for other services provided in primary care, although it has yet to specify them. Charging will also be introduced for emergency services, which are currently exempt, although the government has stressed that no one will be refused treatment in an emergency. The current time scale for testing and introducing charges in primary care is 2015-16. To prevent putting additional pressure on emergency services, charges will not be introduced in emergency care until new systems for identifying chargeable patients are in place and running effectively.

Ethical obligations

So what are the ethical implications of this? What obligations might doctors and society as a whole have to people who happen, for whatever reason, to find themselves in the UK and in need of healthcare? We start with a basic and widely accepted premise: that health is a primary or foundational good—a good necessary to the achievement of a wide range of other human goods. Health of course is not easy to define, being a state more often recognised by its absence. But it is surely uncontroversial that without a minimum level of health our lives will

be restricted, at times severely. It is also uncontroversial that there will be times when access to treatment is necessary to maintain health. Like food and water, there are occasions when it is essential to our wellbeing.

It follows that when someone is in need of something, like food, water, or healthcare, without which he or she is likely to be seriously harmed, and we are in a position to provide it without excessive detriment to ourselves, then provide it we should. (It does not necessarily follow that there is always a duty to provide these things free of charge. Where people have the means to pay and are not eligible for free immediately necessary care, they are under an ordinary obligation to pay for it afterwards. Accepting that the numbers are disputed, where people can afford to travel to the UK solely with the intention of seeking free healthcare to which they are ineligible, charging is appropriate.) This duty is sometimes framed as a “duty” or “right” of rescue and, although not a legally binding duty, finds an echo in current legislation. Under the new proposals, treatment that is “immediately necessary” remains available to all who need it, although charges may be incurred later.

In addition to this primary obligation, the proposed changes also contain some prudential considerations. By keeping GP consultations free, scope exists to identify both communicable diseases and conditions that will deteriorate if untreated, causing avoidable harm and incurring greater costs later on. Understandably, many doctors will feel uncomfortable about restricting access to free healthcare. Setting aside administrative problems—who will do the assessments, for example, and on the basis of what presenting criteria—two things are crucial: assessment of whether treatment is “immediately necessary” must always be a matter for professional judgment. And the provision of treatment and the processes for charging must be kept separate. Doctors are providers of healthcare. They are not, and must not be forced to become, immigration officers.

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