

# RESEARCH

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## WHAT OUR READERS ARE SAYING

### **Muscular strength in male adolescents and premature death**

In this cohort of 1 142 599 Swedish male adolescents aged 16-19 years followed over a period of 24 years, muscular strength—as assessed by knee extension and handgrip tests—was associated with a 20-35% lower risk of death from all causes and cardiovascular disease before age 55, independent of body mass index or blood pressure. Stronger adolescents had a 20-30% lower risk of death from suicide and were 15-65% less likely to have any psychiatric diagnosis (such as schizophrenia and mood disorders), say the authors.

Here's how David Goldsmith and Daniel Leckström from Imperial College London responded:

"The main debate seems to centre on two considerations. Firstly, just how easy is it to disentangle the discrete and relevant impacts of body weight, muscle strength, aerobic fitness, and personal 'motivation' on the overall performance these young male potential recruits achieved? And secondly, just how generalisable might these findings be to adolescent men from other countries? The findings are available uniquely because of the Swedish societal system. We think that a case could be made for a randomised controlled trial of a carefully calibrated "intervention" for 16-18 year olds whose attainments in these types of assessments are particularly unimpressive. But which priorities should be set—a focus on aerobic fitness, muscular strength, BMI, smoking, or mental health/self esteem? Or should researchers try to target all of these at once?"

### **General health checks in adults for reducing morbidity and mortality from disease**

According to this Cochrane systematic review and meta-analysis, general health checks do not reduce morbidity or mortality, neither overall nor for cardiovascular or cancer causes, although they increased the number of new diagnoses. Important harmful outcomes were often not studied or reported, say the authors.

**Johannes Scholl, a specialist in internal medicine, responded:**

"This meta-analysis just shows that screening procedures or health checks without appropriate measures (such as evaluations of fitness and metabolic risk) and without individual lifestyle coaching are ineffective. This should not be interpreted as ineffectiveness of preventive healthcare."

**And physician Harald Lipman responded:**

"Merely performing health checks solely reveals actual or potential problems and in the absence of subsequent measures to treat or reduce the risk of developing ailments is not going to show any beneficial effect on morbidity or mortality. Does meta-analysis of trials of periodic health checks assess whether such measures were initiated?"

## RESEARCH ONLINE

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### **Comorbidity in patients with branch retinal vein occlusion**

In this case-control study with prospective follow-up data from Danish national registries, diabetes, hypertension, and peripheral artery disease were associated with an increased risk of developing branch retinal vein occlusion up to a decade later. Branch retinal vein occlusion was associated with an increased risk of subsequently developing hypertension, diabetes, congestive heart failure, and cerebrovascular disease, emphasising the importance of preventive initiatives. These results fit the assumption that branch retinal vein occlusion is a consequence of arterial thickening and that the arteriovenous crossing signs that precede it are hallmarks of arterial disease, say the authors.



# Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies)

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## STUDY QUESTION

What was the survival and morbidity to discharge from hospital in extremely premature babies in England in 2006 and had outcomes changed since 1995?

**SUMMARY ANSWER** 1041 of 2034 (51%) babies born alive between 22 and 26 weeks' gestation in 2006 survived, and 423 of 1041 (41%) survivors were free from major morbidity. From 1995 to 2006 survival of babies born between 22 and 25 weeks' gestation who were admitted for neonatal intensive care increased but the proportion of survivors with major neonatal morbidity was similar.

**WHAT IS KNOWN AND WHAT THIS PAPER ADDS** Mortality and morbidity after extremely preterm birth are high. This study shows that admissions and survival have increased, thus the absolute numbers of survivors both with and without major morbidity has increased.

## Participants and setting

All births in England between 22 to 26 weeks' gestation in 2006 and admissions to English neonatal units of babies who were born between 22 and 25 weeks in 1995.

## Design, size, and duration

Prospective national cohort studies: EPICure comprised 666 babies admitted to neonatal units who were born between 22 and 25 weeks' gestation in March to December 1995 and EPICure 2 comprised 3133 total births between 22 and 26 weeks' gestation in January to December 2006. Detailed maternal and neonatal clinical data were recorded for all births in 2006 by using the 1995 dataset with supplementary questions.

## Main results and the role of chance

In 2006, of 3133 total births, 2326 (74%) were of babies known to be alive at the onset of labour; of these, 2034 (87%) were born alive (56% at 22 weeks increasing to 98% at 26 weeks;  $P<0.001$ ). Active care at birth was withheld for

73% (111/152) at 22 weeks, 16% (55/338) at 23 weeks, and <2% thereafter. Survival of babies who were born alive increased from 2% ( $n=3$ ) at 22 weeks to 19% ( $n=66$ ) at 23 weeks, 40% ( $n=178$ ) at 24 weeks, 66% ( $n=346$ ) at 25 weeks, and 77% ( $n=448$ ) at 26 weeks ( $P<0.001$ ). Of the babies who survived, 68% ( $n=705$ ) had bronchopulmonary dysplasia, 13% ( $n=135$ ) had serious abnormality on cerebral ultrasonography, and 16% ( $n=166$ ) had received laser treatment for retinopathy of prematurity.

From 1995 to 2006, admissions to neonatal intensive care of babies born between 22 and 25 weeks' gestation increased by 44%. Survival increased by 9.5% at 23 weeks' gestation (confidence interval -0.1% to 19%), 12% at 24 weeks (4% to 20%), and 16% at 25 weeks (9% to 23%). The proportion treated for retinopathy increased from 13% to 22% ( $P=0.006$ ); the proportions with other morbidities were similar.

## Bias, confounding, and other reasons for caution

Guidance for calculation of gestational age changed between 1995 and 2006, but using different methods had only minor effects on the results. Adherence to evidence based interventions increased in 2006 and was reflected in improved condition shortly after birth; after adjustment for early condition, predictors of death and morbidity were similar between the cohorts.

## Generalisability to other populations

In England neonatal care is organised into networks but in 2006, 42% of extremely preterm births took place outside designated tertiary centres. International differences in the organisation of services and of active interventions around the time of birth, particularly for babies born between 22 and 23 weeks' gestation, might affect the generalisability of these survival data.

## Study funding/potential competing interests

The study was funded by the Medical Research Council (G0401525).

**Births and survival of babies born between 22 and 26 weeks' gestation in England during 2006. Figures are percentages (95% confidence intervals)**

	Gestation at birth (weeks)				
	22	23	24	25	26
Total births (including all stillbirths)	478	594	636	692	733
Survival to discharge:					
No of babies	3	66	178	346	448
% of live births	2 (0 to 6)	19 (15 to 24)	40 (36 to 45)	66 (62 to 71)	77 (73 to 81)
% of admissions	16 (3 to 40)	30 (24 to 37)	47 (41 to 52)	69 (65 to 74)	78 (75 to 82)
No (%) of survivors without major morbidity*	1 (33, 1 to 91)	15 (23, 13 to 35)	52 (29, 23 to 37)	133 (38, 33 to 44)	222 (50, 45 to 54)

\*Defined as any of severe abnormality on cerebral ultrasonography, severe bronchopulmonary dysplasia, retinopathy of prematurity stage 3 or more, or laparotomy for necrotising enterocolitis.

# Neurological and developmental outcome in extremely preterm children born in England in 2006 and 1995: the EPICure studies

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## STUDY QUESTION

What are the outcomes at age 3 years for babies born extremely preterm (22-26 weeks' gestation) in England during 2006, and what changes have occurred in outcomes since 1995 for babies born between 22 and 25 weeks' gestation?

## SUMMARY ANSWER

Survival to age 3 years for extremely preterm babies admitted for intensive care increased by 13% from 1995 to 2006 (39% to 52%), and 11% more babies survived without disability (23% to 34%).

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Clinical decisions at birth for extremely preterm babies rely on information about the risks of impairment. The high risk of serious impairment at age 3 years persisted in preterm babies born in 2006 and increased as gestation shortened, from 20% of survivors at 26 weeks' gestation to 45% at 23 weeks.

## Participants and setting

1031 surviving babies born before 27 completed weeks' gestation in 2006 to mothers in England. Outcome evaluation was blinded to the clinical neonatal course of the child (n=576) or taken from routine assessments done locally (n=191); outcomes for those not evaluated were imputed. We compared outcomes between 584 children born at 22-25 weeks' gestation in 2006 and 260 surviving children born in 1995.

## Design, size, and duration

Prospective national cohort studies: EPICure (births from March to December 1995) and EPICure 2 (January to December 2006). Babies born in 2006 were evaluated at a median age of 34 (range 27-48) months or outcomes evaluated at a median age of 25 (18-50) months and obtained from local records. Data collection was censored at 42 months because of the tests used. Evaluation comprised the Bayley scales of infant and toddler development (third edition), a neurological evaluation and neurosensory function, graded according to current recommendations. For

comparison with 1995 data we used a published algorithm to adjust the developmental test scores.

## Main results and the role of chance

The prevalence of moderate or severe impairment in survivors ranged from 45% at 22-23 weeks' gestation to 30% at 24 weeks, 25% at 25 weeks, and 20% at 26 weeks; 14% of the cohort had cerebral palsy, most with mild or moderate functional impairment. Mean predicted mental development index quotients were 89 (SD 19) after adjustment; mean adjusted scores ranged from 80 (21) at 22-23 weeks' gestation to 87 (19) at 24 weeks, 88 (19) at 25 weeks, and 91 (18) at 26 weeks ( $P<0.001$ ). Since 1995 a trend to increased survival with severe disability (2.6%, 95% confidence interval -2.3% to 7.5%) was matched by an increase in the proportion of admissions surviving without disability (11%, 6% to 16%), particularly for babies born at 24 weeks (10%, 0.5% to 20%) and 25 weeks (15%, 6% to 24%).

## Bias, confounding, and other reasons for caution

Evaluation of the 2006 cohort at age 3 years was delayed by changes in data protection and research governance and censored at 42 months of age. We imputed outcomes as the perinatal characteristics of the population had been completely ascertained. Comparison of developmental scores with births in 1995 was confounded by a change in the nature and structure of the developmental test.

## Generalisability to other populations

The findings of this study represent outcomes for the whole geographical population; in other settings organisational and policy differences may modify results. Subsequent developments in neonatal care will require evaluation against outcomes.

## Study funding/potential competing interests

This study was funded by the Medical Research Council (G0401525). The funder had no role in the study design, analysis, interpretation of data, or writing of the report. We have no competing interests.

Percentage (95% confidence interval) of extremely preterm babies born during 2006 in England and surviving without moderate or severe impairment based on population alive at onset of labour, proportion offered active care after delivery, and those admitted for neonatal care

Outcomes	Gestational age at birth (weeks)				
	22	23	24	25	26
Alive at onset of labour	0.4 (0 to 2)	8 (5 to 11)	23 (19 to 27)	44 (39 to 49)	60 (55 to 65)
Live birth with stabilisation attempted	2 (0 to 13)	12 (8 to 16)	27 (22 to 32)	47 (42 to 53)	62 (57 to 67)
Admissions for neonatal care	5 (0 to 26)	15 (10 to 21)	30 (25 to 35)	49 (43 to 55)	62 (57 to 67)

# Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing: prospective randomised trial in Finland

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Research: Cost effectiveness of human papillomavirus test of cure after treatment for cervical intraepithelial neoplasia in England: economic analysis from NHS Sentinel Sites Study (*BMJ* 2012;345:e7086)

Research: Risk of cervical cancer after completed post-treatment follow-up of cervical intraepithelial neoplasia: population based cohort study (*BMJ* 2012;345:e6855)

## STUDY QUESTION

Does human papillomavirus (HPV) screening detect precancerous cervical lesions earlier than conventional cytology screening, without substantially increasing the overall burden of follow-up and treatment in screened women?

## SUMMARY ANSWER

Compared with cytology, HPV screening could increase the overall burden of cervical precancerous lesions slightly, if age groups and screening intervals are selected properly.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Primary HPV DNA screening detects cervical lesions earlier than conventional screening, but brings a risk of increased detection of non-progressive lesions, adding to the overall burden. With a proper selection policy, HPV tests can detect precancerous lesions earlier and increase the overall burden of the disease in the target population only slightly.

## Design

Prospective randomised trial with computer generated allocation (1:1) to primary HPV DNA tests followed by cytology triage, or to conventional cytology screening (Pap testing). The screening method was disclosed to participants at the screening visit. The personnel involved were aware of all test results.

## Participants and setting

Women aged 25-65 years were invited for screening in 2003-07 (101 678 screened initially by HPV DNA test, 101 747 by Pap test), based on a population based programme for cervical cancer screening in Finland. Eligible women underwent one screening round of five years.

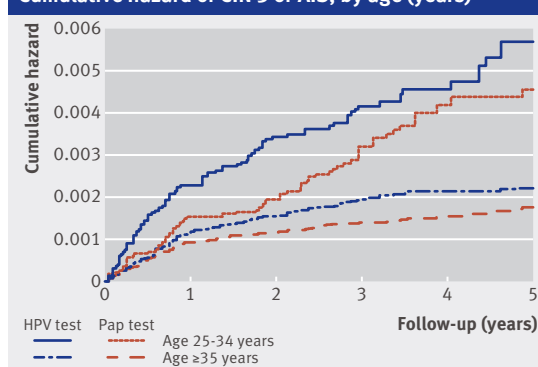
## Primary outcome(s)

Hazard ratios and cumulative detection rates of cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS), and cervical cancer detected before the second screening visit (after five years) or 31 December 2008. Lesions detected at screening and during the interval were included during an average follow-up of 3.6 years.

## Main results and the role of chance

We detected 1010 and 701 lesions in the HPV and conventional arms, respectively. Compared with conventional screening, hazard ratios were 1.53 (95% confidence interval 1.28 to 1.84) for CIN grade 1, 1.54 (1.33 to 1.78) for CIN 2, 1.32 (1.09 to 1.59) for CIN 3 or adenocarcinoma in situ, and 0.81 (0.48 to 1.37) for cancer. In women aged 25-34 years, the cumulative hazard (that is, the cumulative detection rate) of CIN 3 or AIS was 0.0057 (0.0045 to 0.0072) for those who underwent

Cumulative hazard of CIN 3 or AIS, by age (years)



HPV screening, compared with 0.0046 (0.0035 to 0.0059) for conventional screening. Corresponding cumulative hazards in women aged 35 years and older were 0.0022 (0.0019 to 0.0026) and 0.0017 (0.0014 to 0.0021), respectively.

## Harms

Many CIN lesions were detected in women younger than 35 years, and these were detected by HPV tests substantially more often than by cytology screening. When introducing primary HPV screening, it would be essential to monitor screening, reduce opportunistic testing, and study new management strategies, especially in young women.

## Bias, confounding, and other reasons for caution

Cervical cancer incidence was lower in the HPV arm than in the conventional arm among women who did not attend screening. Some women may have requested information about the screening method beforehand, which could have influenced their decision to take the HPV test. We could not identify errors in the randomisation process, nor could we rule out pure chance. The more sensitive primary screening test (that is, the HPV DNA test) will identify more cervical lesions at the initial screening visit which will be treated, leading to different disease prevalences (occurrence of pre-invasive lesions) between the arms. Thus, opportunistic Pap testing favours disease detection in the conventional arm, with fewer cervical lesions detected initially and with higher residual incidence, and hence preferentially improves the Pap test performance.

## Generalisability to other populations

Results indicate test performance within the healthcare system (including large opportunistic screening), and therefore extrapolations to other environments should be done with caution.

For funding statement see *bmj.com*



# Impact on health inequalities of rising prosperity in England 1998-2007, and implications for performance incentives: longitudinal ecological study

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Research: Use of relative and absolute effect measures in reporting health inequalities: structured review  
(*BMJ* 2012;345:e5774)

Research: Income inequality, mortality, and self rated health: meta-analysis of multilevel studies  
(*BMJ* 2009;339:b4471)

## STUDY QUESTION

Did the local authorities in England that saw the greatest rise in prosperity in the boom decade of 1998-2007 experience the greater rises in life expectancy, and what were the implications for health inequalities?

## SUMMARY ANSWER

English local authorities with the greatest improvement in prosperity had greater increases in life expectancy, and health inequalities between the most deprived local authorities and all local authorities widened.

## WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Rising national prosperity in England over the decade from 1998 to 2007 was associated with increasing average life expectancy for the country as a whole. The uneven rise in prosperity between 1998 and 2007 accounted for differential increases in life expectancy in English local authorities; however, the more deprived an authority was in 1998, the lower the rate at which life expectancy improved, independent of changes in prosperity.

## Participants and setting

We used data on residents of 324 local authorities in England.

## Design, size, and duration

This longitudinal ecological study used regression analysis to investigate the association between trends in prosperity (measured by unemployment, household income, and educational achievement) from 1998 to 2007 and trends in life expectancy, and whether baseline deprivation influenced the trend in life expectancy. Data came from the NHS Information Centre and the Office for National Statistics. The level of deprivation in each local authority at the start of this time period in 1998 was measured by the Indices of Multiple Deprivation 2000.

## Main results and the role of chance

With each 1% absolute decline in unemployment, men's life expectancy increased by 2.2 (95% confidence interval 0.5 to 3.8) months and women's by 1.7 (0.4 to 3.1) months over the decade studied. With each £1000 increase in average household income in a local authority, men's life expectancy increased by 1.4 (0.3 to 2.5) months and women's by 1.1 (0.2 to 1.9) months. Local authorities that were more deprived at the beginning of this time period had significantly smaller improvements in life expectancy, even when the changes over time in unemployment and household income were taken into account. The combined effect was a widening of health inequalities between the more deprived (Spearhead) local authorities and all local authorities over the decade.

## Bias, confounding, and other reasons for caution

We cannot rule out reverse causality, in which local authorities with greater improvements in health have greater potential for increased prosperity. Our results could be explained by confounding factors; however, plausible factors such as environmental or neighbourhood improvements are also likely to be related to overall improvements in prosperity. Population migration between local authorities over time may also have influenced the results, although other studies indicate that this effect is likely to be small.

## Generalisability to other populations

The results are generalisable to other countries within the United Kingdom and would have relevance to other developed countries concerned about the effect of macro-economic conditions on health inequalities.

## Study funding/potential competing interests

BB is supported by an NIHR doctoral research fellowship (DRF-2009-02-12). DT-R is supported by an MRC population health scientist fellowship (G0802448).

Effect of baseline deprivation, decrease in unemployment, and increase in average household income on increase in life expectancy		
Factor influencing life expectancy	Increase in life expectancy —months (95% CI)*	P value
<b>Men (<math>R^2=0.27</math>)</b>		
Additional increase in life expectancy with each 1% decline in unemployment rate	2.2 (0.5 to 3.8)	0.009
Additional increase in life expectancy with each £1000 increase in disposable household income per head	1.4 (0.3 to 2.5)	0.01
Additional increase in life expectancy for each point that LA's initial level of deprivation (IMD2000) is lower than average	0.2 (0.1 to 0.3)	<0.001
<b>Women (<math>R^2=0.28</math>)</b>		
Additional increase in life expectancy with each 1% decline in unemployment rate	1.7 (0.4 to 3.1)	0.013
Additional increase in life expectancy with each £1000 increase in disposable household income per head	1.1 (0.2 to 1.9)	0.016
Additional increase in life expectancy for each point that LA's initial level of deprivation (IMD2000) is lower than average	0.3 (0.2 to 0.4)	<0.001
IMD2000=Indices of Multiple Deprivation 2000; LA=local authority. *95% CI based on robust standard errors; model adjusted for nine government office regions.		