

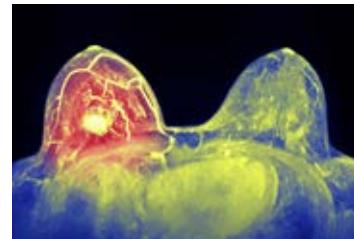
# research



Genetic evidence links better education with lower risk of Alzheimer's disease p 395



Exposure to air pollution from road traffic adversely affects fetal growth p 396



Dutch mammography screening has little impact on the burden of advanced breast cancers p 398

## ORIGINAL RESEARCH Mendelian randomisation analysis

### Modifiable pathways in Alzheimer's disease

Larsson S C, Traylor M, Malik R, et al, for the CoSTREAM Consortium, on behalf of the International Genomics of Alzheimer's Project

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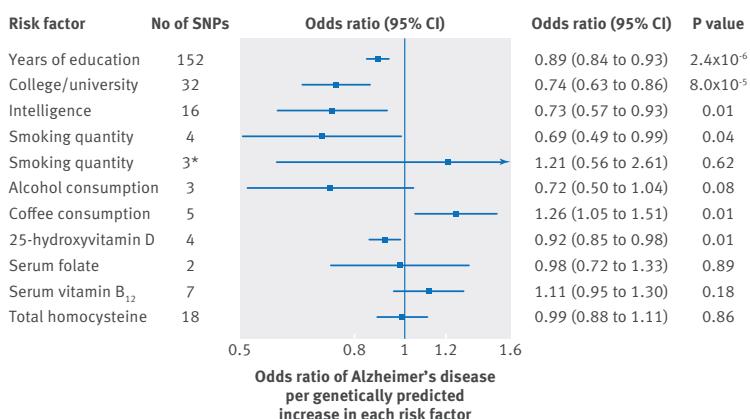
Find this at: <http://dx.doi.org/10.1136/bmj.j5375>

**Study question** Which are the potentially modifiable risk factors for Alzheimer's disease?

**Methods** Mendelian randomisation analyses to assess the association between 24 potentially modifiable risk factors and Alzheimer's. Summary statistics data for the associations of the single nucleotide polymorphisms with the modifiable risk factors were obtained from genome-wide association studies of the risk factors and from the International Genomics of Alzheimer's Project (17 008 cases and 37 154 controls).

#### Study answer and limitations

Genetically predicted educational attainment was inversely associated with Alzheimer's, with odds ratios of 0.89 (95% confidence interval 0.84 to 0.93;  $P=2.4\times10^{-6}$ ) per year of education completed and 0.74 (0.63 to 0.86;  $P=8.0\times10^{-5}$ ) per unit increase in log odds of having completed college/university. There was no evidence that alcohol consumption, serum folate, serum vitamin B<sub>12</sub>,



Odds ratios for associations between genetically predicted higher educational attainment, intelligence, and lifestyle and dietary factors and Alzheimer's disease. Estimates are per year of education completed, 1 unit higher log odds of college/university completion, 1 SD higher intelligence, 10 cigarettes/day, drink of alcohol/week, cup of coffee/day, 20% increase of 25-hydroxyvitamin D concentration, and 1 SD serum folate, serum vitamin B<sub>12</sub>, and total homocysteine.  
\*Excludes one outlying genetic variant (rs1051730) in or near neuronal nicotinic acetylcholine receptor genes (CHRNA3, CHRNA5, and CHRNB4). SNPs=single nucleotide polymorphisms

homocysteine, cardiometabolic factors, and C reactive protein were associated with Alzheimer's, but suggestive associations ( $P<0.05$ ) were observed for intelligence, smoking, concentrations of 25-hydroxyvitamin D, and coffee consumption. A limitation is that a pleiotropic or direct causal pathway cannot be ruled out as explanations for the observed associations.

**What this study adds** This study provides more support for the association between higher

educational attainment and lower risk of Alzheimer's disease.

**Funding, competing interests, data sharing** This study was supported by the European Union's Horizon 2020 research and innovation programme and the Swedish Brain Foundation. Individual authors have support from Cambridge University Trusts National Institute for Health Research (NIHR) Biomedical Research Centre, a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society, and a NIHR senior investigator award. There are no competing interests and no additional data available.

# Traffic pollution is linked to poor pregnancy outcomes

## ORIGINAL RESEARCH Retrospective population based cohort study

### Impact of London's road traffic air and noise pollution on birth weight

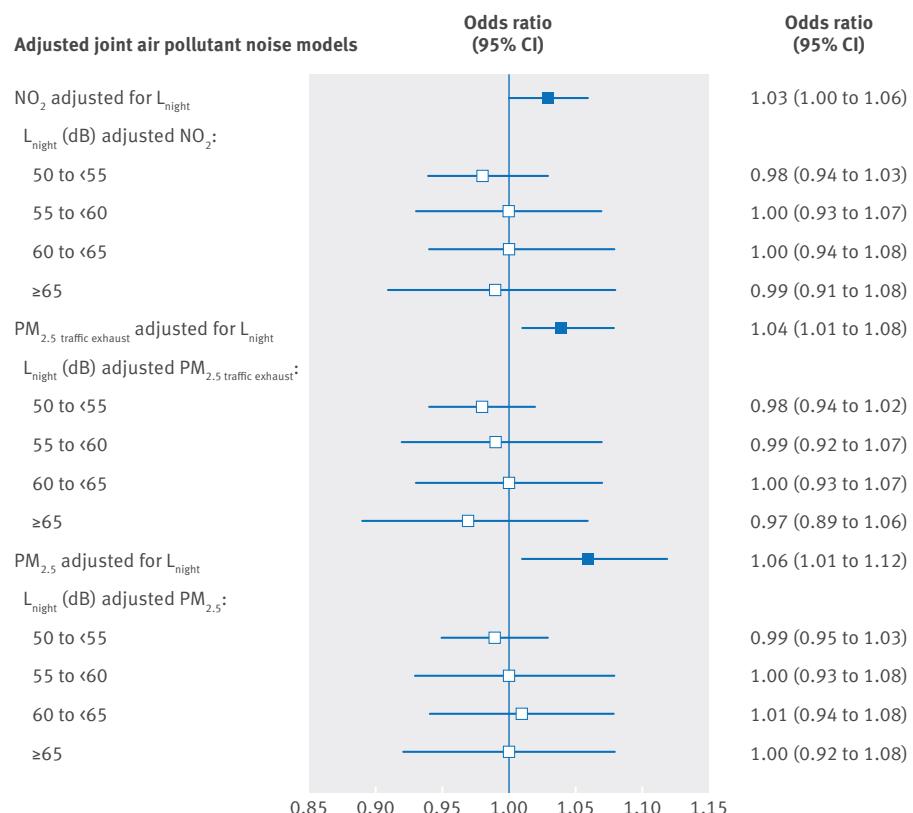
Smith R, Fecht D, Gulliver J, et al

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**Study question** Is exposure to road traffic related air and noise pollution during pregnancy associated with low birth weight (LBW)?

**Methods** This was a retrospective population based cohort study comprising a population of 540 365 singleton term live births in the Greater London area from 2006 to 2010. The authors assessed the risk of term LBW, term small for gestational age (SGA), and mean difference in term birth weight associated with average air pollutant (nitrogen dioxide ( $\text{NO}_2$ )), nitrogen oxides ( $\text{NO}_x$ ), total particulate matter with diameter  $<2.5 \mu\text{m}$  ( $\text{PM}_{2.5}$ ), total particulate matter with diameter  $<10 \mu\text{m}$  ( $\text{PM}_{10}$ ),  $\text{PM}_{2.5}$  from traffic exhaust ( $\text{PM}_{2.5 \text{ traffic exhaust}}$ ),  $\text{PM}_{2.5}$  from traffic non-exhaust ( $\text{PM}_{2.5 \text{ traffic non-exhaust}}$ ), and ozone ( $\text{O}_3$ ) exposures during pregnancy and road traffic noise exposure at residential address at birth. Exposures were examined singly and jointly, with adjustment for potential confounding.



Odds of term low birth weight (LBW) associated with air pollutants (for each interquartile range (IQR)) and night-time noise ( $L_{night}$ ) in selected adjusted joint exposure models. Odds ratios for night-time noise ( $L_{night}$ ) are versus the reference group <50 dB

### COMMENTARY Only policy makers have the power to protect women and unborn babies

In this issue, Smith and colleagues report that air pollution from road traffic, but not traffic noise, is associated with low birth weight at term.<sup>2</sup> The inference is that reducing exposure to air pollution from road traffic will not only improve the health of current adult populations, but has the potential to reduce the burden of non-communicable diseases in future generations too.

The association between air pollution, pregnancy complications, and childhood illness is not new. Exposure to small particle pollution in pregnancy has previously been linked to fetal growth,<sup>3</sup> as well as preterm birth,<sup>4</sup> stillbirth,<sup>5</sup> and respiratory morbidity in children.<sup>6</sup>

#### Increasing awareness without solutions for risk reduction may serve only to increase maternal anxiety and guilt

However, while these associations are biologically plausible, underlying causal mechanisms are not yet established. Smith and colleagues distinguish between particulate matter from primary exhaust pollution and from other sources of particle pollution, which is a helpful step towards isolating sources and composition of particle pollution that are most harmful.<sup>2</sup>

In addition, Smith and colleagues attempt to distinguish between traffic air pollution and traffic noise pollution.<sup>2</sup> Previous studies of noise pollution in pregnancy have provided conflicting results,<sup>7</sup> so it is reassuring to see that

there is no evidence of an independent detrimental effect of traffic noise on birth weight.

#### Compelling evidence of harm

With compelling evidence of harm from environmental air pollution, pregnant women should consider how to reduce their risk. Air filtering facemasks might reduce acute exposure to particulate pollution,<sup>8</sup> but there is no evidence that they reduce chronic exposures. Other strategies include changes to walking routes away from major roads and avoiding outdoor activity when air quality is at its poorest. However, the ubiquity of poor air quality in urban areas like London mean that personal behaviour changes are unlikely to result in substantially different long term exposures. Such lifestyle changes are not realistic for many pregnant women, owing

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### Study answer and limitations

Interquartile range increases in  $\text{NO}_2$ ,  $\text{NO}_x$ ,  $\text{PM}_{2.5}$ ,  $\text{PM}_{10}$ ,  $\text{PM}_{2.5}$  traffic exhaust, and  $\text{PM}_{2.5}$  traffic non-exhaust were associated with increased odds of term LBW (2% to 6%) and SGA (1% to 3%), after adjustment for road traffic noise.

Trends of decreasing birth weight with increasing exposure to road traffic noise were not robust to adjustment for traffic related air pollutants. It was estimated that 3% of term LBW cases in London are directly attributable to residential exposure during pregnancy to  $\text{PM}_{2.5} > 13.8 \mu\text{g}/\text{m}^3$ . Study limitations included the potential for exposure misclassification and residual confounding.

**What this study adds** Exposure to local air pollution from road traffic is associated with an increased risk of LBW in London, but there is little evidence for an independent exposure-response effect of traffic related noise on birth weight.

**Funding, competing interests, data sharing**  
See bmj.com for funding. The authors have no competing interests. No additional data are available.



to constraints from employment patterns, residential location, and transport options. These constraints are highest in those who are socioeconomically disadvantaged, contributing to health inequalities.

Women are therefore reliant on policy change to reduce the risk to their unborn baby from air pollution. In the context of a less than encouraging UK government response to air quality, *The BMJ* has previously noted the need to tackle the issue of highly polluting vehicles in urban areas.<sup>9</sup>

The example from Beijing, where air quality levels were improved during the 2008 Olympics after aggressive government interventions to cut vehicle emissions and industrial production, shows what can be achieved with coordinated action. The immediate positive effects of such interventions were pronounced enough for

improvements in population birthweight to be detected.<sup>10</sup>

The challenge is to maintain reductions in the longer term through combinations of national and local authority action, particularly around reducing congestion and implementing interventions to tackle diesel combustion emissions in urban areas.

### Public health catastrophe

Though the results reported by Smith and colleagues from the UK are concerning, a global perspective reveals something approaching a public health catastrophe. A recent *Lancet* commission on pollution and health estimated that 16% of all premature deaths worldwide are owing to pollution, with 92% of pollution related deaths occurring in low and middle income countries.<sup>11</sup>

In recent weeks, the city of Delhi, India, has seen air quality reach levels that exceed established scales of measurement, with annual averages of fine particulate matter ( $\text{PM}_{2.5}$ ) 50 times those of London.<sup>12</sup>

Publication of this new study should increase awareness that prenatal exposure to small particle air pollution is detrimental to the unborn child.<sup>2</sup> However, increasing awareness without solutions for risk reduction may serve only to increase maternal anxiety and guilt. Apart from avoiding tobacco smoke, there is little evidence based advice that clinicians can give to women to reduce their risk. Broad, multisector action is urgently required to tackle the problem of air pollution related to traffic, and minimise risks to the health of the next generation.

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## Effectiveness of and overdiagnosis from mammography screening in the Netherlands

Autie P, Bonio M, Koechlin A, Pizot C, Boniol M

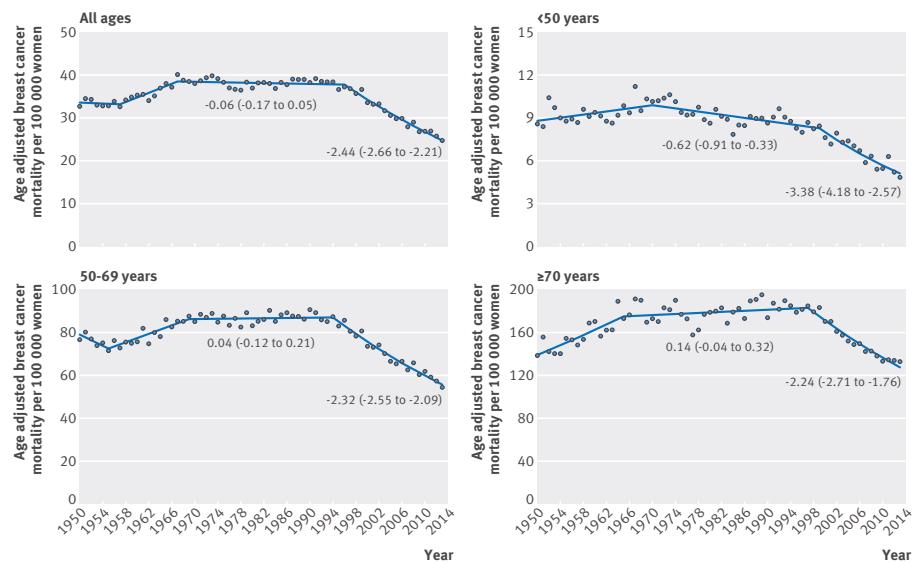
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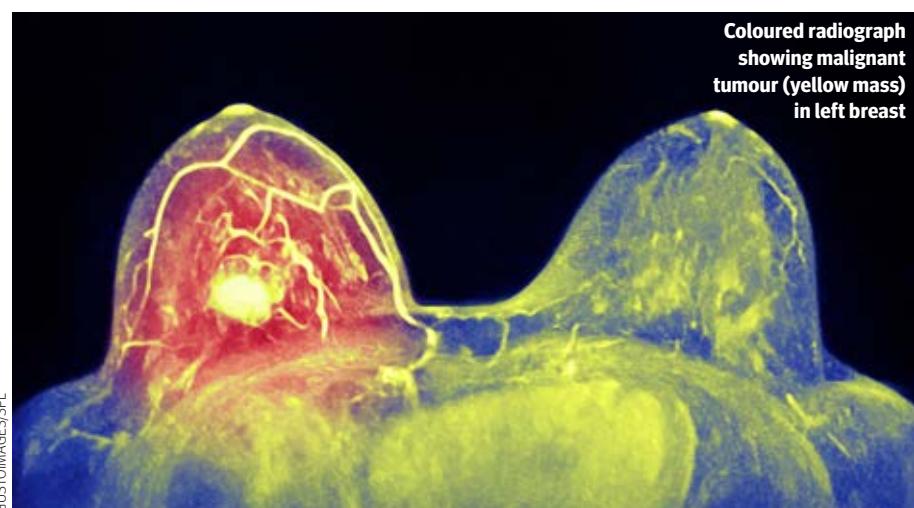
**Study question** What is the stage specific incidence of breast cancer in the Netherlands where women have been invited to biennial mammography screening since 1989, and what is the extent of overdiagnosis?

**Methods** The authors computed stage specific age adjusted incidence rates of breast cancer in Dutch women of all ages and aged 50 or more from 1989 to 2012. They estimated the extra numbers of in situ and stage 1 breast tumours associated with screening by comparing rates in women aged 50-74 with those in age groups not invited to screening. Overdiagnosis was estimated after subtraction of the lead time cancers. Breast cancer mortality reductions during 2010-12 and overdiagnosis during 2009-11 were computed without (scenario 1) and with (scenario 2) a cohort effect on mortality secular trends.

**Study answer and limitations** The incidence rates of stages 2-4 cancers in women aged 50 or more were 168 per 100 000 in 1989 and 166 per 100 000 in 2012. Screening would be associated with a 5% mortality reduction in scenario 1 and with no influence on mortality in scenario 2. In both scenarios, improved treatments would be associated with 28% mortality reductions. After deduction of clinical lead time cancers, 32% of cancers found in women invited to screening in 2010-12 and 52% of screen detected cancers would be overdiagnosed. Because there was no contemporary comparison population with or without low participation in screening, the choice to use trends in women aged



Trends in age adjusted breast cancer mortality by age group in women in the Netherlands, 1950 to 2013. Figures are annual percentage changes (95% confidence intervals) for two last periods with stable trend according to joinpoint analysis



less than 50 and older than 74 was probably the most acceptable surrogate for trends that would have existed in the absence of screening.

**What this study adds** The Dutch mammography screening programme seems to have little impact on the burden of advanced breast cancers, which suggests a

marginal effect on breast cancer mortality. About half of screen detected breast cancers would represent overdiagnosis.

**Funding, competing interests, data sharing** This work was part of internally supported research projects of the International Prevention Research Institute. Data on breast cancer incidence by stage can be requested from the Integraal Kankercentrum Nederland ([www.cijfersoverkanker.nl](http://www.cijfersoverkanker.nl)).

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