

THIS WEEK'S RESEARCH QUESTIONS

- 535** Are men at higher risk than women of developing recurrence of venous thromboembolism?
- 536** Do active smoking and passive smoking increase the risk of breast cancer in postmenopausal women?
- 537** Is cannabis use associated with a risk of later new psychotic symptoms, and is persistent use associated with persistent symptoms?
- 538** How has the provision of effective acute stroke care changed over time in a UK community?
- 539** Have new programmes improved access to medical education for under-represented socioeconomic groups in the UK?

Recurrent venous thromboembolism: are men at higher risk?

Although both sexes have the same risk of a first venous thromboembolism, men appear to be at higher risk than women of a repeat event. However, some large studies have failed to show this supposed association, possibly because of the confounding effects of age (men tended to be older in these studies) and use of hormone therapy by women (which is a reversible risk factor for stroke).

Whether a true link exists is of interest, because if men really are at increased risk, it might be worth keeping them on anticoagulant treatment indefinitely.

James Douketis and colleagues did a meta-analysis of individual patients' data to ascertain the association between sex and recurrence of venous thromboembolism (p 535). They found that men had a 2.2-fold (95% confidence interval 1.7 to 2.8) higher risk of recurrent disease than women after "unprovoked" venous thromboembolism—that is, not associated with a major clinical risk

factor—and the difference remained, albeit somewhat reduced, after controlling for use of hormone therapy by women.

For venous thromboembolism in the presence of a major clinical risk factor (such as cancer or surgery) the risk of recurrence was the same in both sexes. The study also confirmed that the risk of recurrence was reversible in women who took hormone therapy.

Do these findings mean that doctors should treat men and women differently after a first event? Frederick Spencer and Jeffrey Ginberg advise caution (p 508): "Lack of a clear cause for the observed association . . . casts doubt on its clinical relevance." And they note that when this study's risk estimates are applied to the overall risk of recurrence of venous thromboembolism, the gap between the sexes is probably narrower.

Cannabis use and psychosis: which comes first?

Another of this week's studies revisits a question last addressed here several years ago; it's based on data from the early developmental stages of psychopathology (EDSP) study, a German prospective cohort study of which an earlier analysis, published in the *BMJ* in 2005, was among the most read *BMJ* research articles that year (doi:10.1136/bmj.38267.664086.63).

The 2005 article concluded that "Cannabis use moderately increases the risk of psychotic symptoms in young people but has a much stronger effect in those with evidence of predisposition for psychosis." However, years later, whether the association between cannabis use and psychosis is a causal one is still unknown.

Analysing data from the 10 year follow-up wave of the EDSP study, Rebecca Kuepper and colleagues go some way further towards answering the question: they found that cannabis use preceded the onset of psychotic symptoms, and that continued use of the drug might affect the persistence of such symptoms (p 537).



Medical students: access denied?

Jonathan Mathers and colleagues looked at whether programmes developed to widen access to medical education in the UK have produced more diverse student populations, finding that graduate entry programmes had not greatly changed the socioeconomic profile of the medical student population, and that while foundation programmes increased the proportion of students from under-represented groups, the numbers entering these courses were small.

In a rapid response to the paper's online publication, Nicholas Deakin, medical student and former chair of the BMA Medical Students Committee, welcomes the access schemes' "small success stories" but thinks they are "firmly in the shadow of the looming trebling of tuition fees by the current government from £3290 up to a maximum of £9000 per year—despite lively student protests and strong representation from the BMA and others as to the dangers of such a move.

"The Sutton Trust has stated that fear of debt is a major factor for two thirds of students who choose not to pursue higher education. Such debt for medical students already stands at a predicted £37 000 and is predicted to rise to £70 000 . . . a death knell to widening access (<http://bit.ly/en1Lqm>).” *Student BMJ* has more on this issue at <http://bit.ly/gQUNVD>.

LATEST RESEARCH: For this and other new research articles see www.bmj.com/research

Survival with low lung function in cystic fibrosis P M George and colleagues' cohort study of patients in the adult cystic fibrosis unit of London's Royal Brompton Hospital from 1990 to 2007 showed an improvement over the years in the survival of patients with lung function lower than the threshold generally accepted as indicating an increased risk of death within 2 years. A CME learning module accompanies the paper online (doi:10.1136/bmj.d1008).

Quality of chronic disease care for older people Sunil Shah and colleagues compared the care for chronic diseases among older people in care homes with that of care in the community, within the UK Quality and Outcomes Framework pay for performance system. Their retrospective analysis suggests that care for chronic diseases included in QOF, measured by indicators suitable for vulnerable older people, is poorer for residents in care homes than for those in the community (doi:10.1136/bmj.d912).



Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis

James Douketis,^{1,2} Alberto Tosetto,³ Maura Marcucci,⁴ Trevor Baglin,⁵ Benilde Cosmi,⁶ Mary Cushman,⁷ Paul Kyrle,⁸ Daniela Poli,⁹ R Campbell Tait,¹⁰ Alfonso Iorio¹¹

EDITORIAL by Spencer and Ginberg

¹St Joseph's Healthcare Hamilton, Room F-544, 50 Charlton Avenue East, Hamilton, ON, Canada, L8N 4A6

²Department of Medicine, McMaster University, Hamilton

³Department of Hematology, San Bortolo Hospital, Vicenza, Italy

⁴Department of Internal Medicine, Internal and Vascular Medicine, University of Perugia, Perugia, Italy

⁵Department of Haematology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust, Cambridge, UK

⁶Department of Angiology and Blood Coagulation, University Hospital San Orsola-Malpighi, Bologna, Italy

⁷University of Vermont, Burlington, VT, USA

⁸Department of Medicine I, Medical University of Vienna, Vienna, Austria

⁹Thrombosis Centre, Department of Heart and Vessels, University Hospital Careggi, Florence, Italy

¹⁰Department of Haematology, Royal Infirmary, Glasgow, UK

¹¹Departments of Medicine and Clinical Epidemiology and Biostatistics, McMaster University

Correspondence to: J Douketis jdouket@mcmaster.ca

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STUDY QUESTION

In patients with a first episode of venous thromboembolism, are men at higher risk than women of developing recurrence of disease?

SUMMARY ANSWER

Men have a 2.2-fold higher risk of recurrent disease than women after unprovoked venous thromboembolism, but the risk of recurrence after provoked venous thromboembolism is similar in men and women.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Whether men have a higher risk of recurrent venous thromboembolism than do women is uncertain, partly because previous studies did not control for potential sources of bias. The finding of a higher risk in men in a patient level meta-analysis suggests that indefinite anticoagulation should be given greater consideration in men than in women after a first venous thromboembolism.

Selection criteria for studies

Included studies were randomised trials or prospective cohort studies of patients with a first venous thromboembolism with symptoms, who received standardised anticoagulation (five to 10 days of heparin and at least three months of a vitamin K antagonist), were followed up for recurrent venous thromboembolism after anticoagulation was stopped, and had D-dimer measured after anticoagulation was stopped. (The last characteristic was not needed for the analysis reported here but was used for companion studies).

Primary outcome

The primary outcome was risk of recurrent venous thromboembolism in men and women.

Main results and role of chance

We studied 2554 patients with a first venous thromboembolism who had clinical follow-up for a mean of 27.1 (SD 19.6) months. The one year incidence of recurrent venous thromboembolism was 5.3% (95% confidence interval 4.1% to 6.7%) in women and 9.5% (7.9% to 11.4%) in men; the three year incidence of recurrence was 9.1% (7.3% to 11.3%) in women and 19.7% (16.5% to 23.4%) in men. In patients with unprovoked venous thromboembolism, men had a higher risk of recurrence than did women (hazard ratio 2.2, 95% confidence interval 1.7 to 2.8). After adjustment for women with hormone associated initial venous thromboembolism, the risk of recurrence remained higher in men (hazard ratio 1.8, 1.4 to 2.5). In patients with provoked venous thromboembolism, occurring after exposure to a major risk factor, we found no difference in recurrence of disease in men and women (hazard ratio 1.2, 0.6 to 2.4).

PREDICTORS OF RECURRENT VENOUSTHROMBOEMBOLISM (VTE) IN MULTIVARIABLE COX REGRESSION ANALYSIS

Groups of patients for comparison	Risk of recurrent VTE—hazard ratio (95% CI)*
Initial VTE unprovoked (occurring in absence of major antecedent risk):	
Men v all women†	2.2 (1.7 to 2.8)
Men v women (excluding women with previous hormone associated VTE)§	1.8 (1.4 to 2.5)
Women with previous hormone associated VTE v women without previous hormone associated VTE and no other antecedent risk factors	0.5 (0.3 to 0.8)
Initial VTE provoked (occurring in presence of antecedent transient major risk):	
Men v all women†	1.2 (0.6 to 2.4)
Men v women (excluding women with previous hormone associated VTE)‡	1.2 (0.6 to 2.3)

*All estimates came from study stratified Cox regression model with fixed effect.

†Model including age, unprovoked/provoked VTE, interaction between unprovoked/provoked VTE and sex, and proximal/distal VTE as covariates.

‡Model including use/non-use of hormonal therapy, age, unprovoked/provoked VTE, interaction between unprovoked/provoked VTE and sex, and proximal/distal VTE as covariates.

Bias, confounding, and other reasons for caution

Potential unmeasured variables could have affected the risk of recurrent venous thromboembolism, and the study population was predominantly white.

Study funding/potential competing interests

We received no funding for this study.

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Association of active and passive smoking with risk of breast cancer among postmenopausal women: a prospective cohort study

Juhua Luo,¹ Karen L Margolis,² Jean Wactawski-Wende,³ Kimberly Horn,^{1,4} Catherine Messina,⁵ Marcia L Stefanick,⁶ Hilary A Tindle,⁷ Elisa Tong,⁸ Thomas E Rohan⁹

EDITORIAL by Boffetta and Autier

¹Department of Community Medicine, Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV, USA

²HealthPartners Research Foundation, Box 1524, Mailstop 21111R, Minneapolis, MN 55440-1524, USA

³Department of Social and Preventive Medicine, University at Buffalo, Buffalo, NY, USA

⁴WV Prevention Research Center, West Virginia University

⁵Department of Preventive Medicine, Stony Brook University, NY, USA

⁶Stanford University School of Medicine, CA, USA

⁷Center for Research on Health Care, Division of General Internal Medicine, University of Pittsburgh, Pittsburgh, PA, USA

⁸Division of General Internal Medicine, University of California, Davis Medical Center, Sacramento, CA, USA

⁹Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY, USA

Correspondence to: K L Margolis
Karen.L.Margolis@HealthPartners.com

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STUDY QUESTION Do active smoking and passive smoking increase the risk of breast cancer in postmenopausal women?

SUMMARY ANSWER Active smoking was associated with an increase in breast cancer risk, particularly smoking of high intensity, of long duration, and which started at an early age. Extensive passive smoking was also associated with increased cancer risk.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Recent studies have shown an increased risk of breast cancer among women who started smoking at a young age or who smoked for many years. This cohort of postmenopausal women showed an increased risk of breast cancer among smokers, particularly those with high intensity and long duration of smoking, and among lifetime non-smokers with extensive exposure to passive smoking (but no association with lower exposures and no clear dose response to cumulative exposure).

Participants and setting

Women aged 50–79 years enrolled in the Women's Health Initiative Observational Study during 1993–8 from 40 clinical centres in the United States.

Design, size, and duration

79 990 postmenopausal women were followed prospectively to 14 August 2009. In total, 3520 incident cases of invasive breast cancer (all pathologically confirmed) were identified during an average of 10.3 years of follow-up. Detailed, self

reported information on active and passive smoking was collected at baseline.

Main results and the role of chance

Compared with women who had never smoked, former smokers' risk of breast cancer was elevated by 9%, and current smokers' risk was elevated by 16%. Significantly higher breast cancer risk was observed in active smokers with high intensity and duration of smoking, and with initiation of smoking in teenage years. The increased risk of breast cancer persisted for up to 20 years after stopping smoking. Among women who had never smoked, after adjustment for potential confounders, those with the most extensive exposure to passive smoking (≥ 10 years in childhood, ≥ 20 years as an adult at home, and ≥ 10 years as an adult at work) had a 32% excess risk of breast cancer compared with those who had never been exposed to passive smoking (see table). However, there was no significant association in the other groups with lower exposure, and no clear dose response to cumulative passive smoking exposure.

Bias, confounding, and other reasons for caution

This is a large prospective study with pathological confirmation of cases, detailed information on potential confounders, and detailed information on passive smoking, including quantitative measures of exposure in childhood and adult exposure in residential and workplace settings. However, there was possible recall bias with regard to passive smoking in childhood. In addition, data were not collected for the intensity or frequency of passive smoking. The crude measures and potential misclassification of exposure may make our estimate more conservative. The lack of intensity or frequency data also may have hampered our ability to detect a dose-response relation.

Generalisability to other populations

This study supports the hypothesis that active smoking is associated with an increased risk of breast cancer among postmenopausal women. The data also suggest that extensive exposure to passive smoking may increase breast cancer risk. However, since increased risk was restricted to the most extensive passive smoking category with no clear dose response, the association with passive smoking should be considered suggestive only and needs confirmation from other studies.

Study funding/potential competing interests

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RISK OF INCIDENT INVASIVE BREAST CANCER AND EXPOSURE TO SMOKING

Smoking status	No of cases/ participants	Hazard ratio (95% CI)*	Passive smoking†
Never smoked:	1692/41 022	1.00 (reference)	
No exposure to passive smoking	145/3754	—	1.00 (reference)
Exposure to any passive smoking	1515/36 124	—	1.09 (0.92 to 1.29)
Extensive exposure to passive smoking‡	146/2956	—	1.32 (1.04 to 1.67)
Former smokers	1619/33 990	1.09 (1.02 to 1.17)	—
Current smokers	209/4978	1.16 (1.00 to 1.34)	—
Total No of smoking years:			—
<5	220/5398	0.97 (0.84 to 1.11)	—
5–9	182/3987	1.05 (0.90 to 1.22)	—
10–19	401/8306	1.09 (0.98 to 1.22)	—
20–29	387/8208	1.09 (0.97 to 1.22)	—
30–39	341/6708	1.21 (1.07 to 1.36)	—
40–49	178/3864	1.14 (0.98 to 1.34)	—
≥ 50	56/1116	1.35 (1.03 to 1.77)	—
P value for trend		0.0002	—

*Adjusted for potential confounders.

†Analyses performed only among lifetime non-smokers.

‡Exposure in childhood for ≥ 10 years, in adult home for ≥ 20 years, and in adult work for ≥ 10 years.

Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study

Rebecca Kuepper,¹ Jim van Os,^{1,2} Roselind Lieb,^{3,4} Hans-Ulrich Wittchen,^{4,5} Michael Höfler,⁵ Cécile Henquet¹

EDITORIAL by Hall and Degenhardt

¹Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University Medical Center, Maastricht, Netherlands

²King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, UK

³Department of Psychology, Division of Epidemiology and Health Psychology, University of Basel, Switzerland

⁴Max Planck Institute of Psychiatry, Munich, Germany

⁵Institute of Clinical Psychology and Psychotherapy, Technical University Dresden, Germany

Correspondence to: J van Os, Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University Medical Center, PO Box 616, NL-6200 MD, Maastricht, Netherlands
j.vanos@sp.unimaas.nl

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SUMMARY QUESTION

Is cannabis use associated with risk of later, incident psychotic symptoms and does continued use of cannabis increase the risk of persistence of these symptoms?

SUMMARY ANSWER

Cannabis use precedes the onset of incident psychotic symptoms in individuals without any history of psychotic experiences. Continuation of use is associated with risk of persistence of psychotic symptoms in young people.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Cannabis use is associated with an increased risk of psychotic disorder. This study shows the temporal nature of the association, indicating an effect on persistence of symptoms by which cannabis use can increase the risk of psychotic disorder.

Participants and setting

The study was part of the German EDSP study (Early Developmental Stages of Psychopathology), a prospective population based cohort study on the prevalence, incidence, risk factors, comorbidity, and course of mental disorders. The baseline sample consisted of 3021 young people aged 14-24.

Design, size, and duration

The EDSP study is longitudinal and prospective, consisting of a baseline survey and three follow-up surveys, covering average time periods of 1.6 years (baseline to time 1 (T1), SD 0.2), 3.5 years (baseline to time 2 (T2), SD 0.3), and 8.4 years (baseline to time 3 (T3), range 7.3-10.5, SD 0.7). Participants aged 14-17 at baseline were examined at all four time points, and those aged 18-24 were assessed at three time points (baseline, T2, T3). The present study is based on the whole cohort assessed at baseline, T2, and T3. Response rates were 84% (2548) at T2 and 73% (2210) at T3. Cannabis use and psychotic symptoms were assessed with the computerised version of the Munich version of the composite

international diagnostic interview (DIA-X/M-CIDI), an updated version of the World Health Organization's CIDI version 1.2.

A total of 2210 individuals completed the T3 assessment; information on substance use and psychotic symptoms was missing for 287 participants, resulting in a final risk set for analysis of 1923 individuals, of whom 926 (48%) were men. Mean age was 18.3 (SD 3.3) at baseline, 21.8 (SD 3.4) at T2, and 26.6 (SD 3.5) at T3.

Main results and the role of chance

In individuals who at baseline had never displayed any psychotic experience and had never used any cannabis, incident cannabis use over the baseline-T2 period significantly increased the risk of later incident psychotic symptoms over the T2-T3 period (adjusted odds ratio 1.9, 95% confidence interval 1.1 to 3.2, $P=0.02$). Furthermore, continued use of cannabis increased the risk of persistence (that is, psychotic symptoms present at T2 and T3) of psychotic symptoms over the T2-T3 period.

Bias, confounding, and other reasons for caution

All analyses were adjusted for age, sex, socioeconomic status, use of other drugs, childhood trauma, and urban/rural environment. The use of the DIA-X/M-CIDI, which essentially provides self reported information, might have introduced bias. The interview, however, was conducted face to face by psychologists, who were allowed to follow up with clinical questioning to ensure systematic and valid assessment of outcomes and can therefore be assumed to yield better and more valid results than a self report questionnaire.

Study funding/potential competing interests

The EDSP study is funded by grants from the German Ministry of Research, Education and Technology (01EB9405/6 and 01EB9901/6) and the Deutsche Forschungsgemeinschaft (DFG), and this paper is part of NIH grant R01DA016977-01, PL.

CONTINUED CANNABIS USE (FROM BASELINE TO T2 (3.5 YEARS)) AND PERSISTENCE OF PSYCHOTIC EXPERIENCES FROM T2-T3 (8.4 YEARS AFTER BASELINE)

Cannabis continuation	Risk of persistent psychotic experiences	
	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
No use	1	1
At baseline but not at T2	2.0 (0.95 to 4.4), $P=0.068$	2.1 (0.9 to 4.7), $P=0.078$
At T2 but not at baseline	1.9 (1.1 to 3.2), $P=0.022$	1.4 (0.8 to 2.5), $P=0.202$
At baseline and T2	2.6 (1.5 to 4.6), $P=0.001$	2.2 (1.2 to 4.2), $P=0.016$

*Adjusted for age, sex, socioeconomic status, use of other drugs at baseline and T2, childhood trauma, and urban environment.

Provision of acute stroke care and associated factors in a multiethnic population: prospective study with the South London Stroke Register

Juliet Addo,^{1,3} Ajay Bhalla,² Siobhan Crichton,¹ Anthony G Rudd,^{1,2} Christopher McKevitt,¹ Charles D A Wolfe^{1,3}

¹King's College London, Division of Health and Social Care Research, London SE1 3QD, UK

²Department of Health and Ageing, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK

³National Institute for Health Research Comprehensive Biomedical Research Centre, Guy's and St Thomas' NHS Foundation Trust, London, UK

Correspondence to: J Addo
Juliet.addo@kcl.ac.uk

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STUDY QUESTION Has the provision of effective acute stroke care changed over time, and what factors are associated with the provision of such care?

SUMMARY ANSWER Improvement between 1995 and 2009 in the receipt of acute interventions after stroke has been significant although not optimal. Significant inequalities exist in their provision, however, and implementation of evidence based care is not optimal.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Audit reports from a selected sample of patients admitted to hospital suggest an improvement in the quality of stroke care in the United Kingdom over time. This paper provides information on the trends in provision of acute care and the associated factors in a well characterised multiethnic population.

Participants and setting

The study sample comprised 3800 patients of all age groups with a first ever stroke, recorded by the population based South London Stroke Register.

Design

Data were collected prospectively from a community stroke register (1995-2009) with multiple notification sources. We used the χ^2 test for trend to examine trends over time in receipt of acute care interventions, and multivariable logistic regression models to examine the association between sociodemographic as well as case severity variables on the receipt of these interventions.

Primary outcome(s)

Admission to hospital, stroke unit care, appropriate use of acute drugs, and access to rehabilitation therapies.

Main results and the role of chance

Rates of admission to stroke units, brain imaging, and thrombolysis increased significantly over the study period ($P<0.001$). Compared with white patients, black patients had a significantly increased odds of admission to a stroke unit (odds ratio 1.76, 95% confidence interval 1.35 to 2.29, $P<0.001$) and of receipt of occupational therapy or

physiotherapy (1.90, 1.21 to 2.97, $P=0.01$), independent of age or stroke severity. Patients with motor or swallowing deficits were also more likely to be admitted to a stroke unit (1.52, 1.12 to 2.06, $P=0.001$ and 1.32, 1.02 to 1.72, $P<0.001$, respectively). Length of stay in hospital decreased significantly between 1995 and 2009 ($P<0.001$). The odds of brain imaging were lowest in patients aged 75 or more years ($P=0.004$) and those of lower socioeconomic status ($P<0.001$). The likelihood of those with a functional deficit receiving rehabilitation increased significantly over time ($P<0.001$).

Bias, confounding, and other reasons for caution

We adjusted for possible confounders in logistic regression models by including age, sex, ethnicity, and case severity measures. Data were missing for some variables, which could potentially bias the results. However, those with missing data on the intervention variables did not differ significantly from those with complete data on age, sex, ethnicity, and level of consciousness.

Generalisability to other populations

The findings from such a population based study provide representative evidence of stroke care in similar populations with similar provisions of healthcare.

Study funding/potential competing interests

The study was funded by Guy's and St Thomas' Hospital Charity, The Stroke Association, Department of Health HQIP grants, UK, National Institute for Health Research programme grant (RP-PG-0407-10184). The authors (CW) acknowledge financial support from the Department of Health through the National Institute for Health Research (NIHR) Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London and the NIHR research for patient benefit programme award (PB-PG-0407-13228). CDAW is a senior investigator for the NIHR. AGR is funded by the Guy's and St Thomas' NHS Trust AHSC PA Scheme. All researchers are independent of the funders.

INTERVENTIONS IN ACUTE STROKE PHASE OVER STUDY PERIOD

Process measure	1995-7 (n=907)	1998-2000 (n=810)	2001-3 (n=757)	2004-6 (n=706)	2007-9 (n=620)	P for trend
Hospital admission	745/907 (82.1)	693/810 (85.6)	647/757 (85.5)	658/706 (93.2)	587/620 (94.7)	<0.001
Stroke unit admission*	141/736 (18.9)	245/678 (35.4)	424/640 (65.5)	503/644 (76.4)	460/584 (78.4)	<0.001
>50% of stay on stroke unit*	76/733 (10.4)	60/659 (9.1)	306/622 (49.2)	462/642 (72.0)	413/574 (72.0)	<0.001
Median (interquartile range) length of stay (days)	21 (8-52)	21 (8-54)	16 (6-51)	14 (4-37)	13 (5-36.5)	<0.001
Brain imaging	759/891 (85.2)	726/790 (91.9)	678/739 (91.8)	674/685 (98.4)	554/556 (99.6)	<0.001
Swallow test*	710/739 (96.1)	632/682 (92.7)	584/644 (90.7)	594/657 (90.4)	516/587 (87.9)	<0.001

Values are numbers of participants with process/total number with data on process measure (%) unless stated otherwise.

*Analysis limited to patients admitted to hospital.

Widening access to medical education for under-represented socioeconomic groups: population based cross sectional analysis of UK data, 2002-6

Jonathan M Mathers, Alice Sitch, Jennifer L Marsh, Jayne Parry

School of Health and Population Sciences, University of Birmingham, Edgbaston, Birmingham, West Midlands B15 2TT, UK

Correspondence to: J Parry
J.M.Parry.1@bham.ac.uk

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- Analysis: Widening participation in medicine (*BMJ* 2008;336:1111)
- Broadening access to undergraduate medical education (*BMJ* 2000;321:1136)

STUDY QUESTION

Have new medical education programmes such as the graduate entry and foundation programmes changed the socioeconomic demography of the medical student population in the United Kingdom?

SUMMARY ANSWER

The graduate entry programmes have not brought significant changes to the socioeconomic profile of the UK medical student population. Foundation programmes have increased the proportion of students from under-represented groups, but the numbers of students admitted to these courses are small.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Recent years have seen major initiatives in the UK to increase the size and broaden the demography of the medical student population. This study suggests that although historic under-representation of women and of minority ethnic groups has been redressed, most medical students still come from the most affluent socioeconomic groups in society.

Participants and setting

All UK residents who were admitted to one of the 31 UK universities that offered medical degrees during the period 2002-6 (n=34 407).

Design

Population based cross sectional analysis.

Primary outcomes

Age, sex, socioeconomic status, and ethnicity of students admitted to the traditional courses compared with those admitted to the new courses (graduate entry courses and foundation course).

Main results and the role of chance

Overall, three fifths of medical students were female, 71% defined their ethnicity as white, and 39% (13 495) were from higher managerial and professional back-

grounds. Compared with the general UK population, the 2002-6 student population shows over-representation of women and of higher socioeconomic groups and under-representation of students who define their ethnicity as white.

Over 97% of students were enrolled on either traditional or graduate entry programmes. The odds ratio for male students on graduate entry programmes compared with traditional courses was not significant (1.1, 95% confidence interval 0.98 to 1.2; $P=0.107$). Graduate entry students were, significantly older, by an average of 6.9 years (6.8 to 7.1; $P<0.001$), and more likely to be white (3.7, 3.3 to 4.3; $P<0.001$) than traditional students. The demographics of the 325 (<1%) students admitted to foundation courses were different from those on traditional, graduate entry, and pre-medical courses: only 23% (73) of foundation students defined their ethnicity as white and only 8% (24) said their background was higher managerial and professional.

Bias, confounding, and other reasons for caution

Information on socioeconomic status is provided voluntarily by applicants. It was missing in 14% of cases, but this was not constant across the four types of education programme (range 11%-34%).

Generalisability to other populations

We used a national population based administrative dataset from UCAS, the organisation through which applications to university programmes in the UK are processed. We therefore believe that coverage and case ascertainment is near fully complete.

Study funding/potential competing interests

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CHARACTERISTICS OF STUDENTS ADMITTED TO FOUR TYPES OF MEDICAL DEGREE PROGRAMMES, 2002-6

	Traditional (n=30 654)	Graduate entry (n=2948)	Pre-medical (n=480)	Foundation (n=325)	All courses (n=34 407)
No (%) female	18 343 (60)	1710 (58)	324 (68)	202 (62)	20 579 (60)
Mean age (years)	19.2	25.5	22.2	20.9	19.8
No (%) white	21 415 (70)	2462 (84)	405 (84)	73 (23)	24 355 (71)
No (%) from higher managerial/professional socioeconomic group	12 528 (41)	801 (27)	141 (29)	24 (8)	13 495 (39)