

Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke

Stroke Unit Trialists' Collaboration

Abstract

Objectives: To define the characteristics and determine the effectiveness of organised inpatient (stroke unit) care compared with conventional care in reducing death, dependency, and the requirement for long term institutional care after stroke.

Design: Systematic review of all randomised trials which compared organised inpatient stroke care with the contemporary conventional care. Specialist stroke unit interventions were defined as either a ward or team exclusively managing stroke (dedicated stroke unit) or a ward or team specialising in the management of disabling illnesses, which include stroke (mixed assessment/rehabilitation unit). Conventional care was usually provided in a general medical ward.

Setting: 19 trials (of which three had two treatment arms). 12 trials randomised a total of 2060 patients to a dedicated stroke unit or a general medical ward, six trials (647 patients) compared a mixed assessment/rehabilitation unit with a general medical ward, and four trials (542 patients) compared a dedicated stroke unit with a mixed assessment/rehabilitation unit.

Main outcome measures: Death, institutionalisation, and dependency.

Results: Organised inpatient (stroke unit) care, when compared with conventional care, was best characterised by coordinated multidisciplinary rehabilitation, programmes of education and training in stroke, and specialisation of medical and nursing staff. The stroke unit care was usually housed in a geographically discrete ward. Stroke unit care was associated with a long term (median one year follow up) reduction of death (odds ratio 0.83, 95% confidence interval 0.69 to 0.98; $P < 0.05$) and of the combined poor outcomes of death or dependency (0.69, 0.59 to 0.82; $P < 0.0001$) and death or institutionalisation (0.75, 0.65 to 0.87; $P < 0.0001$). Beneficial effects were independent of patients' age, sex, or stroke severity and of variations in stroke unit organisation. Length of stay in a hospital or institution was reduced by 8% (95% confidence interval 3% to 13%) compared with conventional care but there was considerable heterogeneity of results.

Conclusions: Organised stroke unit care resulted in long term reductions in death, dependency, and the need for institutional care. The observed benefits were

not restricted to any particular subgroup of patients or model of stroke unit care. No systematic increase in the use of resources (in terms of length of stay) was apparent.

Introduction

The role of organised (stroke unit) care in managing inpatients with stroke has been controversial for over 30 years.¹ The controversy arises because the moderate benefits that might be anticipated with stroke unit care can be reliably detected (or refuted) only with a very large randomised trial or a proper overview of the available small randomised trials. Evaluation of stroke unit care raises particular problems because of the complex and heterogeneous nature of the intervention and its potential interaction with other aspects of care. Even a prospective multicentre randomised trial could not guarantee a uniform intervention because the service characteristics would inevitably vary between centres.

Systematic review (including meta-analysis) methods combine the available evidence from randomised trials to draw more reliable and generalisable conclusions.² Our review of randomised trials available up to October 1993 indicated that specialist stroke unit care may reduce death and institutionalisation after stroke.³ However, we did not have detailed descriptions of service organisation or detailed information on many outcomes or subgroups of interest and substantial new information has now become available from several recently completed randomised trials.

We conducted a further systematic review to determine whether the apparent benefits of organised stroke unit care were confirmed in a more extensive and updated analysis, examine outcomes in addition to death and institutionalisation, examine the effects in subgroups of stroke patients and with various models of specialist stroke unit care, provide a detailed description of stroke unit and control interventions, and identify the features associated with an improved outcome. To meet these objectives a collaborative review group was formed which included trialists from the available randomised controlled trials.

Methods

We aimed to compare any system of organised inpatient stroke care with the less organised conven-

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A list of collaborators is given at the end of the article.

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tional practice. We therefore included all prospective trials that used some form of randomisation to allocate patients to an organised stroke unit or conventional care, usually in general medical wards. Trials were included if treatment allocation was carried out on a strictly random basis or a quasi-randomised procedure (such as date of admission). We excluded studies which compared specific therapies within an organised stroke care setting.

Our objectives were to examine the effect of organised stroke unit care on the outcomes of death, dependency, and the requirement for institutional care (all recorded at the end of scheduled follow up in an intention to treat analysis).

Identification of trials

We identified relevant research reports up to December 1995 using several approaches.³ In summary, we carried out systematic hand searches of 22 core neurology and stroke journals and five Japanese journals and systematic searches of Index Medicus, Medline, and dissertation abstracts. We searched the reference lists of trials, review articles, and textbooks; Current Contents; and the proceedings of 43 recent conferences on neurology, geriatric medicine, and rehabilitation. Further information was obtained by talking to colleagues and publicising our preliminary findings at stroke conferences in the United Kingdom, Scandinavia, Germany, Switzerland, Spain, Canada, and South America.

Definition of interventions

Although the primary question was whether organised inpatient stroke care could improve outcomes compared with contemporary conventional care, we divided the organisation of service into one of the following three predefined groups to reflect the heterogeneity of services.

Dedicated stroke unit—A service provided by a discrete stroke ward or stroke team working exclusively in the care of stroke patients. This category included acute (intensive) stroke units, which accept patients acutely but discharge early (usually within seven days); rehabilitation stroke units, which accept patients after a minimum delay of seven days and focus on rehabilitation; and combined acute/rehabilitation units, which accept patients acutely but also provides rehabilitation for at least several weeks. Both the rehabilitation unit and combined acute/rehabilitation unit models offered prolonged periods of rehabilitation.

Mixed assessment/rehabilitation unit—A ward or team which has an interest and expertise in the assessment and rehabilitation of disabling illness but does not exclusively manage stroke patients.

General medical wards—A service provided in wards which focus on the management of acutely ill general medical patients but not on their subsequent rehabilitation. In most trials this formed the control group.

Definition of outcome measures

The primary analyses examined death, dependency, and the requirement for institutional care at the end of scheduled follow up. Dependency was categorised into two groups where independent was taken to mean that an individual did not require physical assistance for transfers, mobility, dressing, feeding, or toileting.

Individuals who failed any of these criteria were considered dependent. The criteria for independence were roughly equivalent to a Rankin score of 0-2 or a Barthel score of $>18/20$.⁴ The requirement for long term institutional care was taken as meaning care in a residential home, nursing home, or hospital at the end of the rehabilitation period. Length of stay in a hospital or institution was also recorded.

Data from contributing trials

The principal investigators of all the trials that fulfilled the criteria of the overview were invited to join the Stroke Unit Trialists' Collaboration. All who could be contacted agreed to join. They were asked to provide details of their trial design, including the method of treatment allocation, selection criteria, characteristics of patients, details of service organisation, duration of interventions, duration of follow up, numbers in each outcome group, and additional services after discharge from hospital. The survey of trial characteristics included a structured interview with the trial coordinator, carried out by a single interviewer (PL), which focused on aspects of the structure, staffing, organisation, selection criteria, and procedures and practices within the stroke unit and control settings. For the three trials for which a coordinator could not be contacted we have used the best available published information.

Wherever possible we obtained basic outcome data at the end of scheduled follow up for all patients randomised (to permit an intention to treat analysis). Most trials could be analysed on this basis, at least for the outcomes of death and death or requiring institutional care. Those trials with incomplete follow up were analysed with the assumption that patients lost to follow up were alive and living at home. The implications of these assumptions were explored in a sensitivity analysis.

Outcome information was also sought for subgroups of patients based on age, sex, and stroke severity. Severity of stroke at the time of randomisation was defined by patients' initial dependency (within the first week after stroke). Where randomisation was carried out at different times after stroke, initial dependency was inferred from published information on the expected rate of functional recovery⁵:

Mild stroke—Patient can transfer and walk (with or without assistance) during the first week after the stroke. This is roughly equivalent to a Barthel score of $>10/20$ (Rankin score 0-3) within one week of the stroke or $>13/20$ (0-3) by two weeks after the stroke.

Moderate stroke—Patient is conscious and has sitting balance but is unable to stand or walk during the first week after stroke.

Severe stroke—Patient has reduced consciousness or no sitting balance, or both, during the first week after stroke; equivalent to a Barthel score of $<3/20$ (Rankin 5) within one week or $<4/20$ (5) by two weeks.

Although the inaccuracies inherent in this process are likely to have resulted in some misclassification of patients, the criteria were applied equally to stroke unit and control patients. Most trials used exclusion criteria such that patients with the mildest and severest strokes would be excluded.

We sought individual patient data for all trials, but unfortunately insufficient data were available to permit

Table 1 Characteristics of trials contributing data to the review

Trial	Participants	Comparison groups	Outcomes	Notes
Birmingham ¹⁰	Stroke patients within 2 weeks of a stroke	Intensive rehabilitation in rehabilitation centre MARU (n=29) v normal care in general wards (n=23)	Death and dependency at the end of follow up (6-8 months)	Timing of outcomes not clear. Intervention not defined. 3 control patients lost to follow up
Dover ¹¹	Stroke patients within 9 weeks (most within 3 weeks of a stroke)	DSU in stroke rehabilitation ward (n=116) v geriatric medicine MARU (n=28) or GMW (n=89)	Death, Rankin score, place of residence, length of hospital stay up to 1 year after stroke	Minor randomisation imbalance. Numbers differ slightly from published report following reanalysis of original data. 2 Control patients lost to follow up
Edinburgh ¹²	Acute stroke patients (moderate severity) within 7 days of stroke	DSU in stroke rehabilitation ward (n=155) v GMW (n=156)	Death, dependency, place of residence, length of hospital stay up to 1 year after stroke	6 Intervention and 10 control lost to follow up
Goteborg-Ostra ¹³	Acute stroke patients within 7 days after stroke	Combined acute and rehabilitation DSU within general medical service (n=215) v conventional care in GMW (n=202)	Death, Barthel score, place of residence, length of hospital stay	Not yet published
Goteborg-Sahlgren ¹⁴	Acute stroke patients within 7 days after stroke	Combined acute and rehabilitation DSU v conventional care in GMW	Death, Barthel score, place of residence, patient satisfaction, length of hospital stay up to 1 year	Not yet published
Helsinki ¹⁵	Acute stroke patients, over 65 years age (within 7 days after stroke)	MARU in neurology ward (n=121) v conventional care in GMW (n=122)	Death, Barthel and Rankin scores, length of hospital stay up to 1 year	Intention to treat (on treatment analysis gave less conservative result)
Illinois ¹⁶	Stroke patients up to 1 year after stroke	MARU in rehabilitation service (n=56) v GMW (n=35) which had some specialist nursing input	Functional status and place of residence at end of follow up	Poor definition of services. No deaths reported. 3:2 allocation to intervention:control
Kuopio ¹⁷	Stroke patients (at 1 week after stroke) able to tolerate intensive rehabilitation	DSU in neurological service (n=50) v GMW (n=45)	Death, ADL score, place of residence, duration of hospital stay up to 1 year	Most patients screened failed to meet inclusion criteria for the trial
Montreal ¹⁸	Acute stroke patients with 7 days of a stroke	DSU (mobile stroke team; n=65) v conventional care in GMW (n=65)	Death, Barthel score, place of residence, length of initial hospital stay up to 6 weeks after stroke	Short follow up period. One intervention patient and 3 controls lost to follow up
New York ¹⁹	Stroke patients up to 2 months after stroke	MARU in rehabilitation centre (n=42) v general wards (n=40) with some specialist nursing input	Functional status and place of residence at end of follow up (about 1 year)	No deaths reported. Minor anomaly in published data table
Newcastle ²⁰	Acute stroke patients (within 3 days after stroke)	MARU in geriatric medicine department (n=33) v GMW (n=33)	Death, Barthel and Rankin scores, place of residence, length of hospital stay up to 6 months after stroke	Most patients screened did not meet trial inclusion criteria
Nottingham ²¹	Stroke patients 2 weeks after stroke	DSU (stroke rehabilitation ward) in geriatric medicine department (n=176) v MARU in geriatric medicine department (n=63) or GMW (n=76)	Death, Barthel score, place of residence, length of hospital stay up to 6 months after stroke	Some crossover from GMW to geriatric medicine; 5:4 allocation to intervention:control. 3 Intervention patients and 4 controls lost to follow up
Orpington (1993) ²²	Stroke patients at 2 weeks after stroke	DSU (stroke rehabilitation ward) in geriatric medicine department (n=124) v MARU in geriatric medicine department (n=73) or GMW (n=48)	Death, Barthel score, place of residence, length of hospital stay at end of follow up	Variable duration of follow up
Orpington (1995) ²³	Stroke patients who have a poor prognosis at 2 weeks after stroke	DSU (stroke rehabilitation ward) in geriatric medicine department (n=36) v GMW (n=37)	Death, Barthel score, place of residence, length of hospital stay at end of follow up	Variable duration of follow up. Two control patients lost to follow up
Perth ²⁴	Acute stroke patients within 7 days after stroke	Combined acute and rehabilitation DSU in neurology department (n=28) v GMW (n=30)	Death, Barthel score, place of residence, length of hospital stay up to 6 months after stroke	Most patients screened did not enter trial
Tampere ²⁵	Acute stroke patients within 7 days after stroke (usually earlier)	Acute, intensive DSU in neurology department (n=98) v MARU in a neurology department (n=113)	Death, Rankin score, place of residence, length of hospital stay up to 1 year after stroke	Short duration (1 week) in DSU before transfer to conventional service
Trondheim ²⁶	Acute stroke patients within 7 days (usually within 24 hours) after stroke	Combined acute and rehabilitation DSU (n=110) v GMW (n=110)	Death, Barthel score, place of residence, length of stay in hospital or institution up to 1 year	Intention to treat data used
Umea ²⁷	Acute stroke patients within 7 days of stroke	Combined acute rehabilitation DSU (n=110) v GMW (n=183)	Death, functional status, place of residence, length of initial hospital stay up to 1 year after stroke	Quasi-randomised. Treatment allocation according to bed availability
Uppsala ²⁸	Stroke patients admitted to general medical wards within 3 days of stroke	MARU (organised care within GMW; n=60) v conventional care in GMW (n=52)	Death, ADL score, place of residence, length of stay in acute hospital up to 1 year after stroke	Quasi-randomised. Treatment allocation according to admission rota

Unless otherwise stated, all trials are randomised controlled with balanced allocation to intervention and control groups.

DSU=Dedicated stroke unit (managing stroke patients only), MARU=Mixed assessment/rehabilitation unit (managing other disabling illness as well as stroke), GMW=General medical ward (general medical ward).

a comprehensive individual patient data analysis. The available data were, however, used to cross check the results obtained as summary data.

Statistical methods

Dichotomous outcomes

The formal statistical methods used to combine the results from different trials have been described elsewhere.⁶ Within each trial the standard quantity "observed minus expected" (together with its variance) was calculated for the numbers of events among patients allocated to treatment groups. The grand totals of the individual observed minus expected values and of their

variance were used to calculate P values and odds ratios.⁶ The odds ratio gives the odds of an unfavourable outcome among patients in the treated groups compared with control patients stratified by trial.

This approach (fixed effects model) assumes that each trial result is sufficiently similar to the other results to differ only by chance. Where this is not the case, statistical heterogeneity exists. When heterogeneity was found the sources were explored⁷ and results confirmed by a random effects model analysis.⁸

Continuous variables

Continuous variable data (length of stay) were analysed as the weighted mean difference—that is, the difference

Table 2 Frequency of various characteristics within organised (stroke unit) care and conventional care settings. Values are numbers (percentages) of arms of trials with available data

Characteristics	Organised care	Conventional care	P value*
Disciplines routinely involved in stroke care:			
Medical	22/22 (100)	18/18 (100)	NS
Nursing	22/22 (100)	18/18 (100)	NS
Physiotherapy	22/22 (100)	18/18 (100)	NS
Occupational therapy	21/22 (95)	17/18 (94)	NS
Speech therapy	18/19 (81)	15/18 (83)	NS
Social work	18/19 (81)	17/18 (94)	NS
Coordination of rehabilitation:			
Multidisciplinary team care (weekly meetings)	19/19 (100)	4/19 (21)	<0.0001
Nursing integrated with multidisciplinary team	19/19 (100)	4/19 (21)	<0.0001
Carers routinely involved in rehabilitation	17/19 (89)	2/19 (11)	<0.0001
Carers routinely attend multidisciplinary team meetings	6/18 (33)	0/18 (0)	0.01
Education and training:			
Routine information provision to carers	17/19 (89)	2/19 (11)	<0.0001
Regular staff training	17/20 (85)	1/20 (5)	<0.0001
Specialisation of staff:			
Nursing interest in rehabilitation	18/19 (95)	4/21 (21)	<0.0001
Physician interest in stroke	14/19 (74)	2/19 (11)	0.0001
Nursing interest in stroke	14/19 (74)	2/19 (11)	0.0001
Physician interest in rehabilitation	13/21 (62)	3/21 (14)	0.002
Comprehensiveness of rehabilitation input:			
Increased proportion of patients receive physiotherapy or occupational therapy	9/17 (53)	0/17 (0)	0.0005
Earlier onset of physiotherapy or occupational therapy	7/20 (35)	0/19 (0)	0.004
Medical investigation/treatment protocol	5/19 (26)	0/20 (0)	0.02
Intensity of rehabilitation input:			
More intensive physiotherapy or occupational therapy	8/19 (42)	2/18 (11)	0.03
Enhanced nurse:patient ratio	5/18 (28)	1/17 (6)	NS

*P values were calculated with Fisher's exact test (NS denotes P>0.05)

between mean values in the treatment and control groups of individual trials and the mean difference weighted for trial size for groups of trials.⁹ The 95% confidence intervals of the weighted mean difference were calculated by using the mean and standard deviation data from the individual trials. Because the length of stay was calculated in different ways for different trials, results were calculated from both absolute values (days) and relative change in length of stay (expressed as a percentage of the length of stay in the control group).

Absolute outcomes

Absolute outcome rates, expressed as the proportion of patients in each outcome group are less statistically robust but more clinically meaningful than relative changes in outcomes. The number needed to treat to prevent one adverse outcome was calculated as the reciprocal of the difference in absolute outcome rates between the treatment and control groups.

Results

A total of 19 trials were identified by December 1995.¹⁰⁻²⁸ Seventeen were formally randomised by using random numbers or sequentially numbered sealed envelopes and two used informal procedures based on bed availability²⁷ or a strict admission rota.²⁸ These two trials were evaluated separately to exclude significant bias in the conclusions.

Of the 19 trials identified, one has not yet been completed¹⁴ while the remaining 18 contained a total of 3249 patients. Eleven trials (2060 patients)

compared a dedicated stroke unit with a general medical ward, six (647 patients) compared a mixed assessment/rehabilitation unit with a general medical ward, and four (542 patients) compared a dedicated stroke unit with a mixed assessment/rehabilitation unit (table 1). The total number of comparisons is greater than the number of trials because in three trials patients could be randomised to one of two conventional care groups; two of these trials^{21 22} used a stratified randomisation procedure and one¹¹ did not.

Detailed descriptive information on service characteristics could not be obtained by structured interview for only three trials.^{10 16 19} In 18 trials stroke unit care included rehabilitation lasting several weeks if required; 10 of these units admitted patients acutely and eight after a delay of one to two weeks. Only one trial evaluated an acute stroke unit with no continuing rehabilitation.²⁵

In 17 of the trials the organised care was provided in a geographically discrete ward; two trials examined peripatetic systems of care.^{18 28} Table 2 summarises the service comparisons within the trials. Stroke unit interventions were more likely to be reported to include coordinated multidisciplinary rehabilitation, staff with a specialist interest in stroke or rehabilitation, and regular programmes of education and training. Several factors indicating a more intensive or more comprehensive input of care were less significantly associated with stroke unit care.

Summary data on death, placement, and dependency at the end of scheduled follow up were available for 21, 20, and 20 comparisons respectively. In one trial the number of dependent patients had to be calculated from the mean and standard deviation Barthel score results.¹⁸ Six trials had minor omissions of data during follow up (total 10 stroke unit patients and 25 controls).^{10-12 18 23 27} As these patients were assumed to be alive and living at home, this may have introduced a minor bias in favour of the control group.

Within the stroke unit group 340/1626 (20.9%) patients were dead at the end of follow up (median one year after stroke), 304/1597 (19.0%) were in institutional care, and 519/1409 (36.8%) were dependent. The corresponding figures for controls were 413/1623 (25.4%) dead, 344/1600 (21.5%) in institutional care, and 543/1421 (38.2%) dependent. The minor variation in the denominator is due to placement and dependency data each being unavailable for one trial.

Death only

Figure 1 shows the odds of death by the end of scheduled follow up in different forms of stroke unit versus conventional care. The summary result (odds ratio 0.82, 95% confidence interval 0.69 to 0.98; P<0.05) was not complicated by significant heterogeneity between trials ($\chi^2 = 13.6$, df = 18; P>0.2). There was no detectable variation between the treatment effects in the three subgroup comparisons in figure 1. The odds of death was essentially unchanged if the analysis was restricted to trials where scheduled follow up was continued for a fixed period of six months or one year (0.84, 0.70 to 1.04; P<0.1).^{11 12 15 17 19 20 21 24-28} The exclusion of two trials with an informal randomisation procedure^{27 28} did not affect the conclusions (0.81, 0.67 to 0.98; P<0.05).

Death or institutionalisation

The second outcome examined (fig 2) was the odds of death or requiring institutional care at the end of follow up (median one year after stroke). The summary result (0.75, 0.65 to 0.87; $P < 0.0001$) was highly significant but some heterogeneity existed between trials ($\chi^2 = 25.9$, $df = 19$; $P = 0.1$). Reanalysis of the results with a random effects model produced similar results (0.74, 0.62 to 0.89; $P < 0.0001$). The observed heterogeneity was largely attributable to the five trials that had a short (less than six weeks) or variable period of follow up ($\chi^2 = 14$, $df = 4$; $P < 0.01$).^{13 16 18 22 23} Trials with a fixed follow up period showed a significant reduction in death or institutionalisation (0.76, 0.64 to 0.90; $P < 0.01$) with much less heterogeneity ($\chi^2 = 11.5$, $df = 13$; $P > 0.2$). There was no significant variation between the treatment effects in the three subgroup comparisons. The estimate of apparent benefits was unaffected if informally randomised trials were excluded.

Death or dependency

The third outcome examined was the combined adverse outcome of being dead or dependent in activities of daily living at the end of follow up (fig 3). The overall odds ratio of being dead or dependent if given stroke unit care rather than conventional care was 0.71 (0.61 to 0.84; $P < 0.0001$) but the summary result showed some heterogeneity ($\chi^2 = 16.1$, $df = 19$; $P > 0.2$). Reanalysis with a random effects model produced similar results (0.72, 0.61 to 0.83; $P < 0.0001$). The main source of heterogeneity seems to reflect the nature of the control group. Results were less heterogeneous ($\chi^2 = 10$, $df = 12$; $P > 0.2$) and odds ratios remained significant (0.66, 0.55 to 0.79; $P < 0.0001$) where either a dedicated stroke unit or a mixed assessment/rehabilitation unit was compared with a general medical ward. The conclusions were not altered by the exclusion of trials with a variable follow up period^{10 18 22 23} or informal randomisation procedure^{27 28} or where numbers of dependent patients were calculated from continuous data.¹⁸

The main methodological difficulties with using dependency as an outcome was the degree of blinding of the final assessment and the potential for bias if the assessor was aware of the treatment allocation. Five trials used an unequivocally blinded final assessment for all patients.^{15 17 18 21 27} The odds ratio for death or dependency in that group was 0.72 (0.55 to 0.94; $P < 0.01$).

Absolute outcome rates

The proportion of patients dead at the end of scheduled follow up was 340/1626 (20.9%) in the stroke unit group and 413/1623 (25.4%) in the controls. On this basis the number needed to treat to prevent one death is 22. Interpreting absolute outcome rates can be problematical if the baseline event rate is variable.²⁹ As the baseline fatality rate varied from 0-50% in individual trials the number needed to treat might be expected to range from about 10 to infinity in the different study populations.

The proportion of patients who were unable to live at home at the end of follow up was 640/1597 (40.1%) in the stroke unit group and 755/1600 (47.2%) in the controls (number needed to treat of 14). The baseline

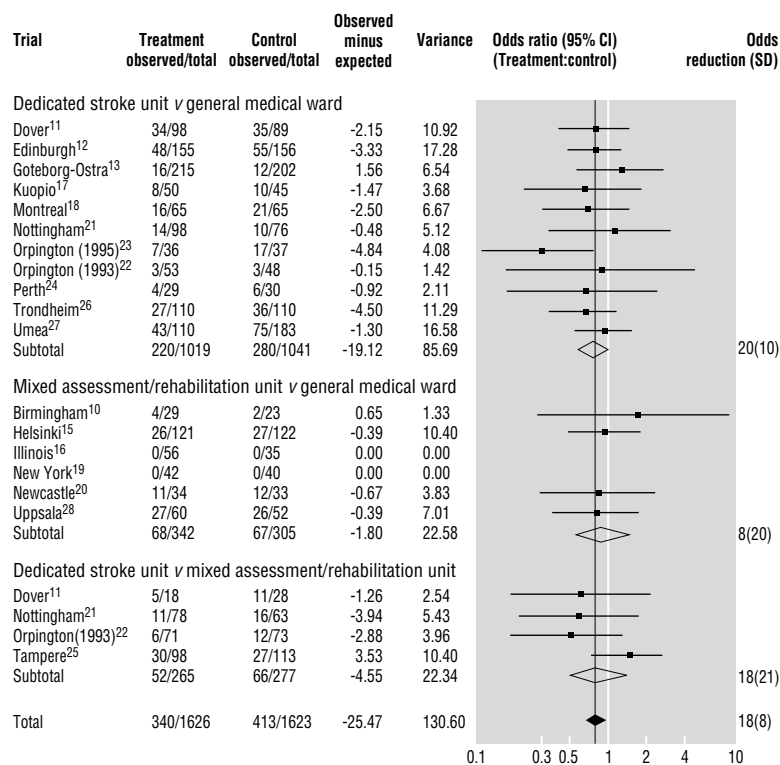


Fig 1 Odds of death occurring by end of scheduled follow up in stroke unit compared with conventional care. Odds ratios and 95% confidence intervals of individual trials are presented as a black box and horizontal line. The pooled odds ratio and 95% confidence interval for a group of trials is represented by an open diamond; the black diamond shows the pooled result for all trials. Data were not available for one trial¹⁴

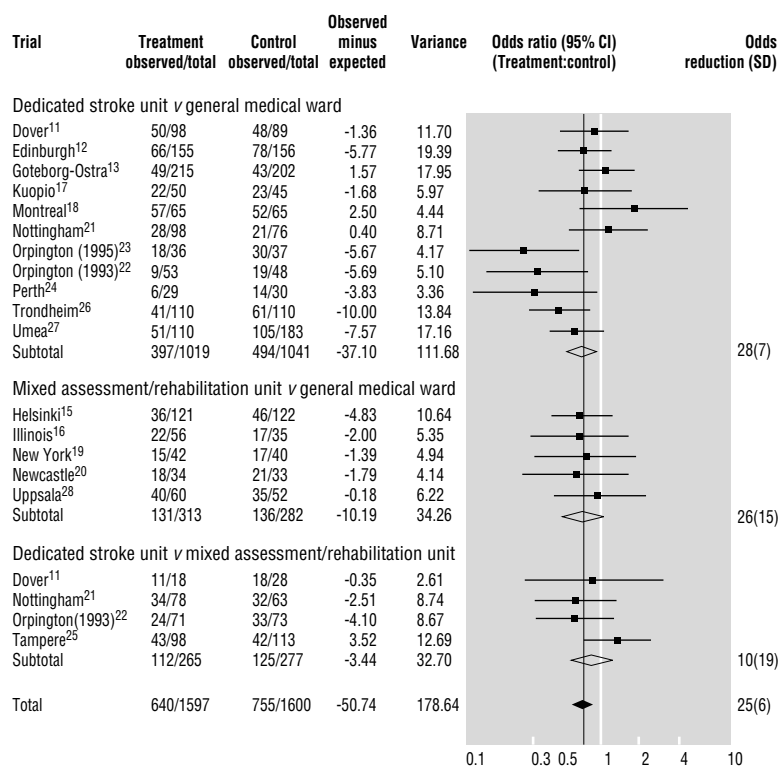


Fig 2 Odds ratio (95% confidence interval) of death or requiring institutional care at the end of scheduled follow up in patients receiving stroke unit compared with conventional care. Abbreviations and terms as for fig 1. Data were not available for two trials^{10 14}

rate in individual trials ranged from 21-81% thus the number needed to treat might range from 8 to 30.

In total 843/1409 (60.0%) stroke unit patients and 944/1421 (66.4%) control patients failed to regain independence (number needed to treat of 16). With baseline rates of death or dependency of 39-100%, the range in the number needed to treat would be about 10 to 25.

Length of stay

Mean or median length of stay was available for 18 trial comparisons. Length of stay was calculated in different ways (for example, acute hospital stay, total stay in hospital or institution). Mean length of stay ranged from 13-162 days in the stroke unit groups and 14-137 days in controls. Ten trials reported a shorter length of stay in the stroke unit group^{12 15 22-27} and eight a more prolonged stay.^{11 13 17 18 20 21 28} The calculation of weighted mean differences in length of stay was subject to methodological limitations. Five trials reported median rather than mean length of stay¹³⁻²⁵ and in six trials the standard deviation was inferred from the P value or the standard deviation results from similar trials.^{12 13 22 23 25 26} Overall, there was a relative reduction in length of stay in the stroke unit group of 8% (3-13%). When length of stay was calculated from absolute values (days) there was a non-significant reduction (-0.3, 95% confidence interval -1.8 to 1.1 days). Both the summary estimates were complicated by considerable heterogeneity which limits the extent to which general conclusions can be inferred.

Subgroup analysis

Figure 4 shows the subgroup analyses in terms of relative reduction of the combined adverse outcome of death or requiring long term institutional care. Details

Patient subgroups

Sex:
Male
Female
Age:
<75 years
>75 years
Stroke severity:
Mild
Moderate
Severe

Service subgroups

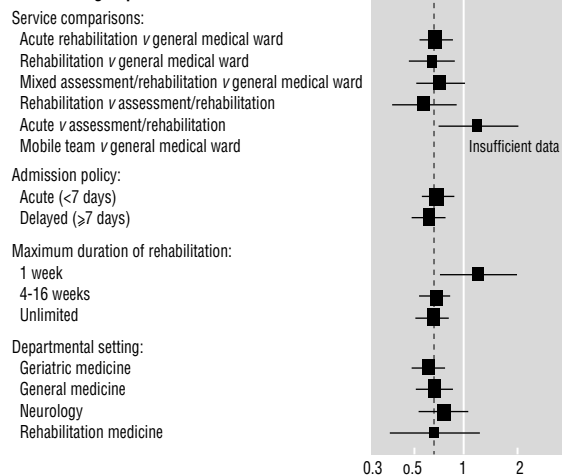


Fig 4 Analysis of patient and service characteristics on effectiveness of stroke unit care versus conventional care. Results are presented as odds ratio (95% confidence interval) of combined adverse outcome of death or requiring long term institutional care. Departmental setting refers to the medical department in which organised stroke unit care was established.

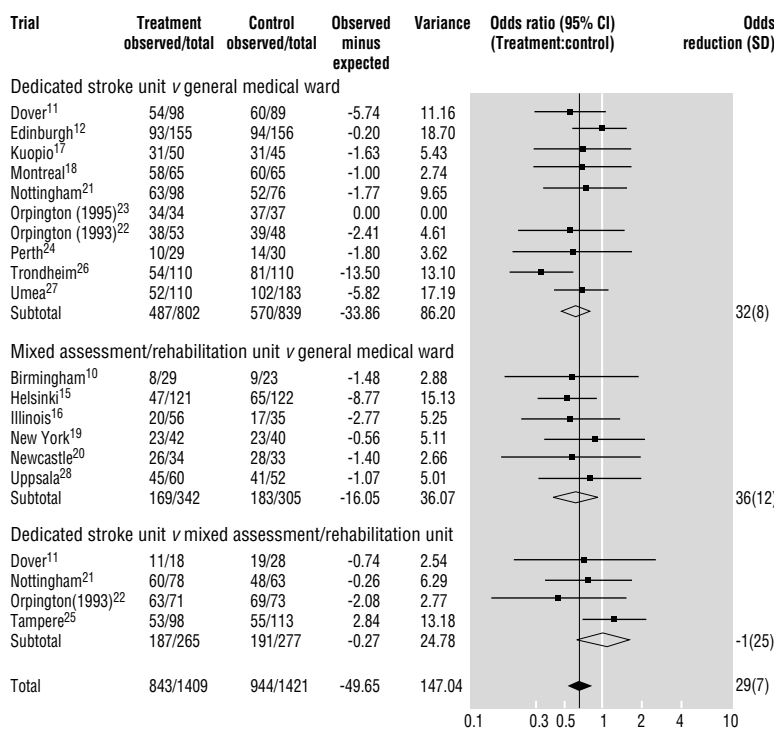


Fig 3 Odds of death or dependency at the end of scheduled follow up with stroke unit compared with conventional care. Abbreviations and terms as for fig 1. Data were not available for two trials^{13 14}

of important subgroups were available for most trials (at least 2000 patients randomised). There was no clear association of the patients' age, sex, or stroke severity with the effectiveness of organised stroke unit care. However, a relatively small number of events were observed, limiting the statistical power.

Figure 4 also outlines the relative reduction in adverse outcomes in a variety of service subgroups. Combined acute/rehabilitation stroke wards, stroke rehabilitation wards, and mixed acute/rehabilitation wards all tended to have better results than conventional care in general medical wards. There were insufficient data to comment on the acute stroke unit and roving stroke team evaluations. Benefits were apparent across units with different forms of admission policy, and within different departmental settings, and across all units which provided rehabilitation.

Publication bias

Publication bias (the selective non-reporting of trial results considered to be neutral or negative) is a potential problem for any systematic review.³⁰ The degree to which the conclusions of the overview would be overturned by missing neutral trials can be estimated by calculating how many randomised patients (with a similar baseline event rate as in the overview) would have to be recruited from neutral trials (odds ratio = 1.0) to render the overall result non-significant (P = 0.05). These estimates for the mortality, combined death and institutionalisation, and combined death and dependency outcomes are >500, >4000, and >6000 respectively. We also examined the distribution

of individual trial results in relation to the trial size in a funnel plot.³⁰ No obvious deficiency of small, negative trials was observed.

Finally we examined the prospective sample of ongoing trials which were identified and recruited before any results were known.^{15 21-25} This included 1558 patients and the odds ratio for the combined outcome of death or institutionalisation was 0.73 (95% confidence interval 0.63 to 0.84; $P < 0.001$).

Discussion

Systematic reviews (including meta-analysis) provide a method for examining the results of randomised trials of interventions which may have modest but clinically important effects.³ There are several potential advantages in having a collaborative review approach, where representatives from each of the original trials are recruited into the study group. Firstly, the network of trialists recruited often have valuable information about unpublished or unfinished randomised trials, thus reducing the risk of publication bias. Secondly, the collaborative approach can allow standardised descriptions of intervention characteristics which would otherwise be reported in a manner which is not sufficiently detailed, standard, or consistent between trials. Thirdly, the collaborative review approach allows the collection of standardised subgroup and outcome information. Finally, interpretation of overviews of complex interventions can be problematical unless one can call on the collective experience and data of the trialists who are aware of the context and practical constraints within which the original randomised trials operated. Overviews based on a reanalysis of individual patient data provide the "gold standard" meta-analysis.³¹ We were not able to pursue this approach because these data were not available for a substantial number of trials. However, we have been able to provide standard data sets and provide much more information than could be obtained from published data alone.

Stroke unit characteristics

Our results indicate that the benefits of organised stroke unit care, as opposed to conventional care, are not clearly due to the structure, departmental setting, staff mix, or the amount of medical, nursing, and therapy input available. The most distinctive features seem to be those of organisation (coordinated multidisciplinary team care, nursing integration with multidisciplinary care, and involvement of carers in the rehabilitation process), specialisation (medical and nursing interest and expertise in stroke and rehabilitation), and education (education and training programmes for staff, patients, and carers). These characteristics were held in common within most stroke unit settings and were usually absent from the conventional care setting. The observation that stroke unit care was usually provided in a geographically discrete ward may reflect difficulties in developing coordinated care within a mobile stroke team.³²

However, several methodological problems exist with this approach to analysing stroke unit services. Firstly, the information was obtained from the trialists who ran the stroke units and we were not able to obtain information from all staff who provided the conven-

tional care. Therefore our findings could be biased by the expectations of the trialists as to which stroke unit features may or may not be effective. Secondly, this was largely a retrospective analysis and in some cases specific questions could not be answered by the trialist or were not explicitly stated in the original published reports. The information provided here may reflect a mixture of both the recollection of factual details and the recall of features which trialists believed were effective. At best, it represents a strictly factual account of service characteristics, while at the worst, it represents a consensus view from the stroke unit trialists as to which features of stroke unit care were important. Although the identification of characteristics which correlate with effective stroke care does not prove that these characteristics dictated that effectiveness, it does provide powerful circumstantial evidence.

Stroke unit outcomes

The primary question of this review was whether organising inpatient stroke care could improve patient outcomes compared with contemporary conventional care. Our results confirm and extend the findings of previous work^{3 33}; compared with conventional care organised stroke unit care reduces the odds of death after stroke. This apparent effect, however, is not statistically robust and could be overturned by a relatively small number of unpublished randomised trials.

The observed reduction in the combined adverse outcomes is much more convincing. The reduction in death or the requirement for long term institutional care was statistically robust. While the requirement for long term care is a useful surrogate for disability that is not subject to assessor bias,³⁴ the absolute rates of institutionalisation will be influenced by national and cultural factors. Our findings indicate that the reduction in the requirement for institutional care was not due to unreasonable hospital discharge policies because the benefits were sustained for up to one year. They also indicate that reduced institutionalisation was a result of fewer patients becoming dependent rather than more dependent patients being discharged home.

The observed reduction in the combined adverse outcome of death or dependency was also statistically robust. However, it is subject to potential observer bias where final assessments were not carried out in a blinded manner. The sensitivity analysis based on those trials which used an unequivocal blinded assessment suggest that such bias has not seriously influenced the results.

Subgroup analysis

The subgroup analysis indicates that the observed benefits of organised stroke unit care are not limited to any particular subgroup of patients or models of stroke unit organisation. The apparent benefits of stroke unit care were seen in both sexes, in patients aged under and over 75 years, and across a range of stroke severities. Combined acute and rehabilitation stroke units, rehabilitation stroke units, and mixed assessment/rehabilitation units all tended to be more effective than conventional care provided in a general medical ward setting. The limited amount of information from direct comparisons of dedicated stroke rehabilitation units with mixed assessment/rehabilitation unit was insufficient to provide conclusive results. Apparent benefits

were seen in units with acute admission policies as well as those with delayed admission policies and in units operating within different departments.

Rational arguments can be made to support individual models of stroke unit care (for example, combined acute/rehabilitation units are likely to cater for a broader group of stroke patients, mixed assessment/rehabilitation units are more flexible in also offering a service to other patient groups). However, our analysis cannot indicate if one model of specialist stroke unit care is more effective than another. The aspects of care which were held in common by all stroke units concerned their provision of prolonged (up to several weeks) periods of rehabilitation and certain practices and procedures (such as the presence of a coordinated multidisciplinary team approach with specialist stroke interests of medical and nursing staff and programmes of ongoing training and education in stroke). All these aspects of stroke unit care are sufficiently fundamental to permit a flexible approach to improving services but are sufficiently specific to allow the audit of such stroke services.

Cost effectiveness

The results reported here indicate that relatively few stroke patients need to be managed in an organised stroke unit to prevent a death, dependency, or institutionalisation. Our calculations of the number of patients needed to treat to prevent one adverse outcome are very approximate. However, they do indicate the potential degree of benefit which might be achieved through improvements in the organisation of stroke patient care. This compares favourably with many routine medical interventions. However, at what cost would this be achieved?

There are insufficient reliable data available to permit a detailed cost effectiveness analysis of stroke unit care, although recent studies from Canada and Europe indicate that the main costs of inpatient stroke care are due to "hotel" and staffing costs.^{35, 36} Therefore the length of stay in hospital may be a good surrogate measure of costs assuming that staffing levels are relatively constant. Our analysis of length of stay was complicated by varying definitions of inpatient stay with variable periods of follow up and different approaches to reporting results. However, the benefits of organised stroke unit care did not depend on an increased hospital stay and may even reduce it. It seems reasonable to conclude that organised (stroke unit) care is unlikely to be more expensive than conventional care in a general ward setting and may be less expensive.

Implications

Acute stroke patients should be offered early organised multidisciplinary care, ideally provided within a ward dedicated to stroke care, which can offer a substantial period of rehabilitation if required. Access should not be restricted by age, sex, or stroke severity. There are several approaches to providing this care but all stroke units should aim to replicate the main characteristics of those in the randomised trials.

Future trials should focus on examining the potentially important components of care and on direct comparisons of different models of organised stroke unit care. Preplanned collaboration between compara-

Key messages

- Previous systematic reviews of organised inpatient (stroke unit) care have been limited by problems of interpretation and characterising stroke unit care
- The important characteristics of stroke unit care within the randomised trials were the provision of coordinated multidisciplinary rehabilitation, staff specialisation in stroke or rehabilitation, and improved education and training
- Patients managed in a stroke unit were more likely to survive, regain independence, and return home than those receiving conventional care
- Apparent benefits were not restricted to any subgroup of stroke patients or model of stroke unit care
- No systematic increase in length of stay was observed

ble trials could alleviate some of the problems of retrospective systematic review.³⁷

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How much alcohol and how often? Population based case-control study of alcohol consumption and risk of a major coronary event

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Abstract

Objective: To quantify the effects of quantity and frequency of alcohol consumption on risk of acute myocardial infarction and coronary death.

Design: Case-control study.

Setting: Lower Hunter region of New South Wales, Australia, 1983-1994.

Subjects: Men and women aged 35-69 years.

Main outcome measure: Acute myocardial infarction or coronary death.

Results: Alcohol consumption patterns were compared between 11 511 cases of acute myocardial infarction or coronary death and 6077 controls randomly selected from the same study population. After adjusting for the effects of age, smoking, and medical history, men and women who consumed one or two drinks of alcohol on five or six days a week had a reduction in risk of a major coronary event compared with men and women who were non-drinkers (odds ratios: men 0.31 (95% confidence interval 0.22 to 0.45); women 0.33 (0.18 to 0.59)). A similar reduction in risk was found after excluding non-drinkers who were formerly moderate to heavy drinkers. An acute protective effect of alcohol consumption was also found for regular drinkers who consumed one or two drinks in the 24 hours preceding the onset of symptoms (odds ratios: men 0.74 (0.51 to 1.09); women 0.43 (0.20 to 0.95)).

Conclusions: Frequency and quantity of alcohol consumption are important in assessing the risk of a major coronary event. Risk is lowest among men who

report one to four drinks daily on five or six days a week and among women who report one or two drinks daily on five or six days a week.

Introduction

Several studies have shown that moderate consumption of alcohol is associated with a reduced risk of coronary heart disease.¹⁻⁵ Other studies have shown little or no association.^{6,7} In these studies subjects were categorised either by the average number of alcoholic drinks consumed per week or in broad groups of light, moderate, or heavy consumption. These methods tend to group together people who have completely different drinking habits—for example, those who have two drinks a day six days a week and those who have a dozen drinks on one day of the week.

We conducted a case-control study to quantify the joint effects of frequency and quantity of alcohol consumed on the risk of a major coronary event. We also investigated the suggestion by Jackson *et al* that moderate consumption of alcohol has an acute protective effect.⁸

Subjects and methods

This study was a product of the World Health Organisation's MONICA project, which monitored trends and determinants in cardiovascular disease in well defined populations in more than 20 countries over 10 years. One such population was subjects aged 35-69 years in Newcastle, Australia.

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Cases were defined as patients who had coronary events which satisfied the criteria for non-fatal definite myocardial infarction, non-fatal possible myocardial infarction, fatal definite myocardial infarction, fatal possible myocardial infarction, or coronary death with insufficient information for further classification.⁹ Information on cases was obtained by following up all suspected coronary events occurring in the study population. This entailed interviewing patients while still in hospital to obtain information on symptoms, medical history, and other variables. Cardiac enzyme activities were extracted from hospital notes and electrocardiograms copied and coded according to the Minnesota code. Details of fatal cases were obtained from death certificates and postmortem records and from doctors, relatives, or other informants. For this study cases were included for the whole period 1984-94.

Controls were participants in risk factor prevalence studies conducted as part of the MONICA project. Those studies were conducted in June to December 1983, June to December 1988 and June to November 1989, and June to December 1994.

For each risk factor study stratified random samples of the study population were selected from the electoral rolls. (In Australia registration on the electoral roll is compulsory for most people.) In 1983 the risk factor survey did not include people aged 65-69 and in 1988-9 and 1994 the sampling fraction was greater for the older age groups. People chosen for the sample were invited to attend study centres to complete a self administered questionnaire and have physical measurements and a blood sample taken. Extensive systems of reminders and follow up were used to encourage participation. The response rate in 1983 was 68%; in 1988-9, 63%; and in 1994, 64%. People who could not attend the centres were asked to complete a brief questionnaire. In 1994 the brief questionnaire included the same questions on frequency and quantity of alcohol consumption as the main questionnaire. This resulted in an increase in the response rate for these items in 1994 from 64% to 75%.

Smoking, age, hypertension, hypercholesterolaemia, diabetes, and a history of angina, acute myocardial infarction, and stroke are associated with an increased risk of acute myocardial infarction. If they are also associated with alcohol consumption, then they are potential confounders to the relation between alcohol consumption and acute myocardial infarction. We therefore adjusted for each of these factors in the analyses.

Subjects were stratified in five year age groups from 35-39 to 65-69. Subjects were deemed to have a history of heart disease if they answered "yes" to either, "Have you ever been told you have had a heart attack/myocardial infarction?" or "Have you ever been told you have angina?" Subjects were deemed to have high blood pressure if they answered "yes" to, "Have you ever been told by a doctor or other medical person that you have high blood pressure?" A similar question was used to ascertain hypercholesterolaemia.

Information about alcohol consumption was obtained by two questions. To determine the frequency of alcohol consumption subjects were asked, "How often do you usually drink alcohol?" Response categories were every day, five or six days a week, three or four

days a week, one or two days a week, less than once a week, rarely, and never. The question on quantity was, "On a day when you do drink alcohol, how many drinks do you usually have?" Subjects were asked to respond in terms of standard drinks (10 g alcohol), using the categories more than 20, 13-20, 9-12, 5-8, 3 or 4, 1 or 2, and "I don't drink." Very few men took more than 20 drinks a day, and they were therefore grouped with those who took 13-20 drinks daily. Similarly for women the categories of more than 20, 13-20, 9-12, and 5-8 were combined to form one category of more than five drinks a day. It was more difficult to obtain information for those who died than for survivors. Data on alcohol consumption were not available for 524 (6.2%) of the 8482 cases who survived and 1422 (46.9%) of the 3029 cases who died.

In the 1994 risk factor prevalence survey an additional category was added to the possible responses to the question on frequency of alcohol consumption. This was, "Used to be a moderate to heavy drinker." The same response category was also included from 1986 for the cases. Using this information we conducted a subgroup analysis with cases from 1991 to 1994 and with controls from the 1994 risk factor survey. In this analysis we separated people who used to be moderate to heavy drinkers from the group of non-drinkers.

To investigate the claim of an acute protective effect of alcohol consumption, we calculated crude and adjusted odds ratios for regular drinkers who consumed 1 or 2, 3 or 4, 5-8, and 9 or more drinks in the 24 hours before the onset of symptoms compared with regular drinkers who did not consume any alcohol in the period. As before, the categories of 5-8 and 9 or more drinks were combined for women. Controls were regular drinkers who participated in the risk factor prevalence surveys, and the exposure variable was their alcohol consumption in the 24 hours before the interview. Regular drinkers were those who reported drinking at least once a week.

Statistics

Initial exploratory analysis entailed comparing cases and controls for factors known to be associated with the risk of a major coronary event. χ^2 Tests were applied to differences in the proportions of cases and controls who had a previous myocardial infarction, angina, stroke, high blood pressure, high cholesterol concentration, or diabetes and to test for an association between case-control status and age group or cigarette smoking.

To measure any difference in risk of a major coronary event associated with alcohol consumption after adjusting for the effects of age, smoking, previous myocardial infarction, angina, stroke, history of high blood pressure, cholesterol concentration, and diabetes odds ratios and 95% confidence intervals were calculated by logistic regression. The base category for alcohol consumption in the analysis was, "I don't drink." Other categories were defined by cross tabulation of the frequency and quantity categories. Logistic regression was performed with the GENMOD procedure in SAS.¹⁰

Table 1 Comparison of cases and controls for factors associated with major coronary event

	No (%) of men			No (%) of women		
	Cases (n=6685)	Controls (n=3027)	P	Cases (n=2880)	Controls (n=3038)	P
Medical history						
Diabetes	808 (12.1)	121 (4.0)	<0.001	507 (17.6)	75 (2.5)	<0.001
High blood pressure	3188 (47.7)	886 (29.3)	<0.001	1809 (62.8)	1093 (36.0)	<0.001
High cholesterol concentration	2463 (36.8)	637 (21.0)	<0.001	1089 (37.8)	546 (18.0)	<0.001
Previous myocardial infarction	1989 (29.8)	198 (6.5)	<0.001	617 (21.4)	80 (2.6)	<0.001
Angina	2769 (41.4)	229 (7.6)	<0.001	1290 (44.8)	126 (4.2)	<0.001
Stroke	543 (8.1)	59 (2.0)	<0.001	280 (9.7)	56 (1.8)	<0.001
Age (years)						
35-39	189 (2.8)	435 (14.4)		43 (1.5)	454 (14.9)	
40-44	387 (5.8)	406 (13.4)		96 (3.3)	424 (14.0)	
45-49	642 (9.6)	412 (13.6)		178 (6.2)	429 (14.1)	
50-54	839 (12.6)	422 (13.9)		290 (10.1)	456 (15.0)	
55-59	1184 (17.7)	434 (14.3)		482 (16.7)	436 (14.4)	
60-64	1654 (24.7)	548 (18.1)		780 (27.1)	526 (17.3)	
65-69	1790 (26.8)	370 (12.2)	<0.001	1011 (35.1)	313 (10.3)	<0.001
Smoking status						
Current smoker	2393 (35.8)	832 (27.5)		778 (27.0)	560 (18.4)	
Former smoker	2882 (43.1)	1128 (37.3)		738 (25.6)	534 (17.6)	
Never smoker	1366 (20.4)	1061 (35.1)	<0.001	1347 (46.8)	1937 (63.8)	<0.001

Results

A total of 11 511 cases were registered by the Newcastle MONICA project during 1984-94 and 6077 controls participated in the risk factor prevalence studies. Of these subjects, 1946 (16.9%) cases and 12 (0.2%) controls were excluded from analysis because of insufficient information on the quantity or frequency of alcohol consumed. Cases excluded from analysis were more likely to be 65-69 years old (34.5% *v* 29.3%; $P < 0.001$), less likely to have survived the event (26.9% *v* 83.2%; $P < 0.001$), and as likely to be male (70.2% *v* 69.9%; $P = 0.79$) as cases who were not excluded.

Table 1 shows that for both men and women cases were significantly more likely than controls to be older, current smokers, and have a history of diabetes, high blood pressure, myocardial infarction, angina, and stroke. The age and sex distribution of controls was determined by the design of the study, so that

adjustment for age and sex differences was necessary for all analyses.

Compared with subjects who did not drink alcohol there was a significant reduction in risk of a major coronary event for men who took one to four drinks daily and women who took one or two drinks daily less than once a week up to five or six days a week (table 2). There was an increased risk of a major coronary event for men and women who took one or two drinks a day rarely and for men who took more than 13 drinks a day on one or two days a week or every day.

After removing former moderate to heavy drinkers from the non-drinking group there remained a reduction in risk of a major coronary event for men who took one to four drinks a day on five or six days a week and for women who took one or two drinks a day on three or four days a week (table 3). Men who took nine or more drinks a day on one or two days a week or

Table 2 Adjusted odds ratios,† 95% confidence intervals, and numbers of cases and controls in each quantity by frequency category of alcohol consumption

	Days per week						
	Don't drink	Rarely	<1	1 or 2	3 or 4	5 or 6	Daily
Men							
Drinks per day:							
Don't drink	1.00 (1634/475)						
1 or 2		1.89 (1.50 to 2.39) (834/133)	0.53 (0.43 to 0.64) (452/325)	0.64 (0.51 to 0.81) (411/218)	0.43 (0.32 to 0.58) (162/133)	0.31 (0.22 to 0.45) (82/108)	0.91 (0.71 to 1.17) (429/141)
3 or 4		1.36 (0.71 to 2.61) (47/15)	0.43 (0.32 to 0.57) (165/164)	0.63 (0.50 to 0.79) (368/231)	0.43 (0.33 to 0.56) (206/175)	0.31 (0.22 to 0.42) (99/123)	0.81 (0.65 to 1.02) (458/181)
5 to 8		0.94 (0.28 to 3.08) (12/5)	1.04 (0.66 to 1.64) (85/38)	0.82 (0.62 to 1.08) (232/116)	0.47 (0.34 to 0.65) (121/99)	0.40 (0.27 to 0.59) (82/66)	0.73 (0.57 to 0.93) (344/158)
≥9			1.57 (0.71 to 3.49) (31/10)	1.58 (0.99 to 2.53) (93/29)	0.89 (0.51 to 1.56) (64/22)	0.86 (0.44 to 1.68) (31/16)	1.43 (0.99 to 2.05) (240/46)
Women							
Drinks per day:							
Don't drink	1.00 (1480/1098)						
1 or 2		1.85 (1.50 to 2.27) (584/265)	0.43 (0.34 to 0.53) (197/608)	0.56 (0.41 to 0.74) (125/260)	0.46 (0.31 to 0.70) (49/144)	0.33 (0.18 to 0.59) (22/96)	0.88 (0.64 to 1.22) (123/132)
3 or 4		1.41 (0.64 to 3.12) (20/19)	0.73 (0.47 to 1.14) (48/113)	0.48 (0.30 to 0.75) (53/99)	0.76 (0.41 to 1.42) (27/43)	0.87 (0.39 to 1.96) (17/18)	0.37 (0.21 to 0.63) (36/61)
≥5		1.62 (0.07 to 35.36) (3/1)	1.17 (0.55 to 2.49) (19/23)	1.60 (0.82 to 3.10) (32/23)	0.82 (0.26 to 2.54) (9/11)	0.14 (0.03 to 0.64) (5/12)	1.34 (0.56 to 3.19) (31/12)

†Odds ratios calculated after adjusting for effects of age, smoking, high blood pressure, high cholesterol concentration, angina, stroke, previous myocardial infarction, and diabetes.

Table 3 Adjusted odds ratios,† 95% confidence intervals, and numbers of cases and controls in each quantity by frequency category with data collected on cases from 1991 to 1994 and controls in 1994

	Days per week						
	Don't drink	Rarely	<1	1 or 2	3 or 4	5 or 6	Daily
Men							
Drinks per day:							
Don't drink	1.00 (319/122)						
1 or 2		1.01 (0.73 to 1.40) 350/133	0.99 (0.66 to 1.50) (151/62)	0.93 (0.62 to 1.37) (167/68)	0.75 (0.45 to 1.25) (69/38)	0.36 (0.19 to 0.66) (27/37)	1.20 (0.79 to 1.82) (158/52)
3 or 4		0.65 (0.29 to 1.45) (21/15)	0.44 (0.25 to 0.78) (45/37)	0.91 (0.58 to 1.42) (101/49)	0.56 (0.35 to 0.90) (69/48)	0.46 (0.27 to 0.80) (43/36)	0.87 (0.56 to 1.33) (139/53)
5 to 8		0.80 (0.22 to 2.96) (8/5)	1.13 (0.54 to 2.35) (32/16)	1.00 (0.59 to 1.70) (71/31)	0.46 (0.26 to 0.82) (34/35)	0.50 (0.26 to 0.96) (31/23)	0.83 (0.53 to 1.30) (115/49)
≥9			0.99 (0.26 to 3.83) (8/4)	2.62 (1.12 to 6.17) (38/8)	1.93 (0.61 to 6.13) (27/4)	2.22 (0.59 to 8.29) (14/3)	2.40 (1.17 to 4.93) (75/11)
Former moderate to heavy drinker	1.06 (0.66 to 1.70) (150/35)						
Women							
Drinks per day:							
Don't drink	1.00 (496/315)						
1 or 2		0.63 (0.47 to 0.84) (205/265)	0.76 (0.48 to 1.20) (54/84)	0.69 (0.43 to 1.11) (49/80)	0.39 (0.19 to 0.82) (13/46)	0.52 (0.23 to 1.16) (14/32)	0.95 (0.54 to 1.69) (37/36)
3 or 4		0.42 (0.13 to 1.34) (6/19)	1.18 (0.50 to 2.82) (15/22)	0.53 (0.22 to 1.28) (12/25)	0.77 (0.24 to 2.50) (10/10)	1.41 (0.27 to 7.26) (5/3)	0.40 (0.16 to 0.98) (13/19)
≥5			1.29 (0.35 to 4.83) (5/7)	2.03 (0.68 to 6.08) (13/7)	1.28 (0.18 to 9.05) (2/3)	0.32 (0.05 to 2.28) (3/5)	2.82 (0.25 to 31.52) (9/1)
Former moderate to heavy drinker	3.90 (0.70 to 21.69) (8/2)						

†Odds ratios calculated after adjusting for effects of age, smoking, high blood pressure, high cholesterol concentration, angina, stroke, previous myocardial infarction, and diabetes.

every day had an increased risk of a major coronary event compared with men who did not drink and were never moderate to heavy drinkers.

Women had a reduced risk of a major coronary event in the 24 hours after consuming one or two alcoholic drinks compared with regular drinkers who consumed no alcohol in the period (table 4). There was a possible reduced risk for men but it was not significant.

Discussion

This study shows that moderate regular consumption of alcohol over five or six days a week is associated with a reduction in risk of a major coronary event. The increased risk for "binge" drinkers compared with non-drinkers is in contrast with the reduction in risk

for those drinking a similar amount a week spread over more days. For example, men who took nine or more drinks a day on one or two days a week consumed similar amounts to those who took three or four drinks a day on five or six days a week but the odds ratios for the two groups were substantially different (2.62 (95% confidence interval 1.12 to 6.17) *v* 0.46 (0.27 to 0.80)).

The biological effects of alcohol depend on how much and how often alcohol is consumed.^{11 12} An increase in blood pressure in drinkers is influenced more by the frequency of consumption than by the quantity consumed.¹¹ Moderate consumption of alcohol causes temporary changes in the fibrinolytic system, which returns to normal within 24 hours.¹² This explains why people who consumed alcohol on five or six days a week had a lower risk of a major coronary event than those who consumed alcohol once a week. It also helps to explain why those who consumed large amounts on one or two days a week did not gain the same benefit as those who consumed similar amounts over five or six days. However, the observation that those who consumed alcohol every day did not seem to have the same beneficial effect suggests that the biological mechanisms of alcohol consumption are more complex than fibrinolytic changes alone. The authors also claimed that the pattern of increase in circulating tissue type plasminogen activator activity, particularly in the morning (13 hours after consumption), may have a protective effect at a time when a large proportion of heart attacks occur.¹² This could explain the protective effect of alcohol consumption in the 24 hours before onset.

Suh *et al* found a positive association between high density lipoprotein cholesterol concentration and consumption of alcohol.¹³ They, however, concluded that the effect of alcohol consumption on high density lipoprotein cholesterol only partly explained the reduction in coronary deaths.

Table 4 Crude and adjusted odds ratios and 95% confidence intervals for risk of major coronary event for each category of number of drinks consumed in 24 hours before onset of symptoms from 1992 to 1994

	Cases	Controls	Odds ratio†	
			Crude	Adjusted
Men				
Drinks in previous 24 hours:				
None	198	166	1.00	1.00
1 or 2	125	156	0.67 (0.49 to 0.92)	0.74 (0.51 to 1.09)
3 or 4	78	76	0.86 (0.59 to 1.25)	1.06 (0.65 to 1.72)
5 to 8	59	62	0.80 (0.53 to 1.20)	0.72 (0.41 to 1.26)
≥9	27	10	2.26 (1.06 to 4.81)	1.46 (0.57 to 3.71)
Total	487	470		
Women				
Drinks in previous 24 hours:				
None	66	156	1.00	1.00
1 or 2	30	140	0.48 (0.27 to 0.84)	0.43 (0.20 to 0.95)
3 or 4	9	30	0.58 (0.25 to 1.39)	0.44 (0.13 to 1.52)
≥5	8	5	2.54 (0.73 to 8.81)	1.15 (0.31 to 7.40)
Total	113	331		

†Odds ratios calculated after adjusting for effects of age, smoking, high blood pressure, high cholesterol concentration, previous myocardial infarction, stroke, angina, and usual alcohol consumption.

Some critics of epidemiological studies that have shown a reduction in the risk of coronary heart disease with moderate alcohol consumption claim that the effect is due to former heavy drinkers or people who are otherwise ill becoming non-drinkers.⁵ In all our analyses we controlled for the effects of history of high blood pressure, angina, stroke, previous myocardial infarction, high cholesterol concentration, and diabetes. This adjustment substantially improved the fit of the model but had little effect on the point estimate for each category of alcohol consumption. Similar results were observed after excluding all cases and controls with a history of acute myocardial infarction, angina, or stroke. Even when former moderate to heavy drinkers were excluded from the analysis there seemed to be a reduction in the risk of a major coronary event for those who consumed a moderate amount of alcohol on three to six days a week. The analysis which excluded previously moderate to heavy drinkers showed no increase in risk among occasional drinkers, and among women who consumed one or two drinks only rarely was there a significant reduction in risk. Thus many previously moderate to heavy drinkers may have reported being occasional drinkers.

Possible confounding factors

A weakness of this study was the large number of cases from whom we did not obtain information on the pattern of alcohol consumption. Of the 1946 cases excluded, 73.1% had died within 28 days after the onset of symptoms. This group may bias the results either in favour of or against a protective effect of alcohol consumption, depending on whether they were more or less likely to be regular drinkers than those included in the analysis.

The validity of self reported alcohol consumption is a possible source of concern in this paper. Romelsjo *et al* showed that the quantity-frequency approach, as used in this paper, resulted in underreporting of alcohol consumption by all sections of the community, women underreporting more than men.¹⁴ General underreporting or overreporting of the quantity of alcohol consumed does not affect the ordinal validity of this study, though it could bias the estimate of threshold levels for "safe" drinking.¹⁵ If women underreported their alcohol consumption more than men this could explain why the reduction in risk for women found in this study was less than the reduction in risk for men.

There was a significant reduction in risk of a major coronary event for women who consumed one or two drinks in the 24 hours before the onset of symptoms and a non-significant reduction in risk for men. This is consistent with the claim by Jackson *et al* of an acute protective effect of moderate alcohol consumption.⁸ This acute protective effect could be a result of changes in fibrinolytic factors which occur within two hours of alcohol consumption¹² and are known to reduce blood clots rather than some cases not drinking in the 24 hour period due to non-specific prodromal symptoms as suggested by Jackson *et al*.

To compare our data with results from other studies we multiplied the average value of each frequency category by the average value of each quantity category to obtain a crude measure of the average number of alcoholic drinks consumed a week. Dividing this result

Key messages

- Alcohol consumption has been associated with a reduced risk of coronary heart disease
- Broad categories of average weekly consumption of alcohol do not take into account the importance of frequency of consumption
- A new study shows that men and women who consume one or two alcoholic drinks a day on five or six days a week have a substantially reduced risk of coronary heart disease
- Alcohol consumption is associated with an acute protective effect for 24 hours
- Adverse physical and social effects of alcohol consumption should prevent consumption of alcohol being recommended as a health measure

by 7, we categorised subjects as consuming none, less than 1, 1 or 2, 2-4, 4-7, or more than 7 drinks a day. Comparing the risk of acute myocardial infarction for each of these categories with the risk for those who were non-drinkers, we found a similar U shaped curve as reported elsewhere, with the lowest risk for men who consumed two to four alcoholic drinks a day (odds ratio 0.63; 95% confidence interval 0.53 to 0.76) and for women who consumed two to four alcoholic drinks a day (odds ratio 0.54; 0.36 to 0.82). Though these results are consistent with those of other investigators,^{1,3,4} they obscure the different effects of frequency and quantity of alcohol shown in tables 2 and 3.

Despite the results of this and other studies caution is needed in promoting alcohol consumption because the adverse effects of abuse may well outweigh any potentially beneficial effect in reducing heart disease. This paper is intended to clarify understanding of the biological effect alcohol consumption has on coronary heart disease and provide a better understanding of the aetiology of the disease.

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Ecological analysis of collectivity of alcohol consumption in England: importance of average drinker

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Abstract

Objective: To assess whether the average consumption of alcohol is associated with the prevalence of heavy drinking, problem drinking, and abstinence in England.

Design: Ecological analysis using data from a cross sectional household based survey of English adults.

Subjects: Random sample of 32 333 adults from the English population who participated in the 1993 and 1994 health surveys for England.

Main outcome measures: Association, expressed as the correlation coefficient, between the regional mean and median alcohol consumption and the regional prevalence of heavy drinking, problem drinking, and abstinence.

Results: Mean consumption of alcohol in light to moderate drinkers was strongly positively associated with the prevalence of heavy drinking ($r=0.75$ in men and $r=0.62$ in women for drinking more than 21 and 14 units per week respectively). A similar association was found between median consumption and prevalence of heavy drinking. Abstinence was not significantly associated with mean consumption in drinkers ($r=0.08$ for men and $r=-0.29$ for women). Both the median and mean consumption in drinkers were positively associated with the prevalence of problem drinking as defined by the CAGE questionnaire on alcohol use ($r=0.53$ for men and $r=0.42$ for women for the association with mean consumption).

Conclusion: Factors that increase the average consumption of alcohol in the population may result in an increase in the prevalence of heavy drinking and related problems.

Introduction

There has been widespread criticism of the British government's increase in the definition of the upper limit of sensible drinking to between 3 and 4 units a day for men and between 2 and 3 units a day for women.^{1,2} The Interdepartmental Working Group considered that there was little evidence of harm at these rates of consumption and pointed to the possible benefits of light drinking on the risk of cardiovascular disease.¹ However, the single population theory, as

propounded by Rose, Ledermann, Skog, and others, states that the distribution of alcohol consumption moves up or down as a whole and that drinking behaviour is under "collective influence."³⁻⁵ If the theory is correct it suggests that any increase in mean consumption is likely to lead to an increase in the prevalence of heavy drinking. Indeed, a separate working group of the royal colleges considered that public health would be affected adversely if mean consumption were to increase.⁶

The single population theory has been supported most convincingly by an analysis correlating mean consumption and the prevalence of heavy drinking across 32 centres participating in the Intersalt study.³ However, several important questions remain unresolved, which we address in this paper using data on alcohol consumption across English regions.

Firstly, as was pointed out in the Interdepartmental Working Group's report,¹ whether such between country differences will also be seen within a country such as the United Kingdom is unclear.

Secondly, the theory suggests that an increase in mean consumption would also lead to a decrease in the prevalence of abstinence, something that has not been consistently shown. This is particularly important for public health as an increase in the prevalence of light consumption and a corresponding reduction in abstinence could result in a reduction in cardiovascular disease in some age groups.⁷

Thirdly, as women who drink heavily are more likely than men to drink at home the degree of collectivity of consumption among women might be less than among men, but this question has not been specifically examined.^{8,9}

Finally, the single population theory has been criticised as being simply a statistical artefact on the grounds that mean consumption and the prevalence of heavy drinking must be correlated as a higher proportion of heavy drinkers will inevitably increase mean consumption.¹⁰ Our analysis addresses this criticism by removing heavy drinkers from the calculation of mean consumption and also by analysing the association between median consumption and the prevalence of heavy drinking. As an alternative approach we also used a measure of problem drinking,

the CAGE questionnaire on alcohol use, which does not directly contribute to the mean.

Subjects and methods

The health survey for England is an annual household based survey that is carried out across all regions in England. The methods have been fully described elsewhere.^{11 12} We used data on 32 333 adults who participated in the 1993 and 1994 health surveys for England to calculate the mean alcohol consumption and the prevalence of heavy drinking and abstinence for each of the former 14 regional health authority areas. The survey entailed an interview, during which respondents were asked about how much and how often they had drunk alcohol over the previous 12 months. This was used to estimate weekly consumption. The method is the same as that used in the general household survey.¹³ The invited sample was representative of the total English adult population in age, sex, regional distribution, socioeconomic status, and ethnic group. A new sample is invited each year, so the data for 1993 and 1994 are independent. The household response rate was 81% in 1993 and 77% in 1994. The response rate varied from 77% in the North East Thames region to 85% in the East Anglia region. Within regions the interviewed sample was representative of the age, sex, and social class of the total population of the region.

Sex specific mean consumption was correlated against the proportion of heavy drinkers across regions. Correlations were examined visually in scatter plots and were summarised using least squares linear regression weighted by the sample size in each region. The strength of the association was given by the correlation coefficient and the slope of the association by the regression coefficient for a unit difference in mean consumption (see table 2).

As the definition of heavy drinking is to some degree arbitrary, we used several definitions, thereby examining the sensitivity of the results to different thresholds. Three thresholds were used—the previous recommended limits (above 21 and 14 units per week for men and women respectively); the new daily benchmarks averaged over a week (28 and 21 units); and the value defining the highest 10% of consumption for both men and women as this affects a similar

proportion of men and women, unlike the other definitions. The analysis was carried out with and without heavy drinkers contributing to the mean, thereby reducing the degree of inbuilt correlation between the mean and the proportion of heavy drinkers. As the median may be a better measure of the central tendency for a skewed distribution, we also examined the association between the median consumption among drinkers and the prevalence of heavy drinkers. The use of the median consumption also has the advantage that, provided the median is below the threshold for defining heavy drinking (which it is), it will not have an inbuilt correlation with the prevalence of heavy drinking.

The association between mean and median consumption in drinkers and the prevalence of non-drinkers was examined by the same method. Those who had never drunk and those who had not drunk any alcohol in the previous year were classified as abstainers. For this analysis abstainers were excluded from the calculation of the mean and median as the mean and median for the total population have an inbuilt correlation with the prevalence of abstinence.

We also examined the relation between mean and median consumption among drinkers and a measure of problem drinking that does not contribute directly to the calculation of the mean. Problem drinking was defined as a score of two or more on a modified CAGE questionnaire on alcohol use of six items,¹⁴ which has been used in other population surveys.⁹ Three of the questions examine physical dependence (being unable to stop drinking, drinking to steady nerves, and having shaking hands on the morning after drinking) while the others concern social attitudes to drinking (feeling guilty, feeling you should cut down, being annoyed at others' criticisms of your drinking). We hypothesised that the questions on physical dependence were less likely than the others to be influenced by the extent of the acceptance of drinking in a culture and may therefore provide a more independent measure of problem drinking for the purpose of this analysis. We therefore examined the association between the mean and median consumption in drinkers and the prevalence of physical dependence (a score of at least one on these three questions).

Table 1 Mean consumption of alcohol and prevalence of heavy drinking and abstinence in total population by region

Region	Men				Women			
	No of respondents	Mean No of units/week	No (%) of abstainers	No (%) drinking >21 units/week	No of respondents	Mean No of units/week	No (%) of abstainers	No (%) drinking >14 units/week
Northern	1027	22.7	51 (5.0)	395 (38.5)	1267	7.5	136 (10.7)	208 (16.4)
Yorkshire	1151	18.2	77 (6.7)	380 (33.0)	1353	6.3	155 (11.5)	190 (14.0)
North Western	1205	19.5	107 (8.9)	411 (34.1)	1416	7.3	187 (13.2)	212 (15.0)
Mersey	756	19.9	29 (3.8)	262 (34.7)	896	6.7	93 (10.4)	125 (14.0)
Trent	1581	16.8	123 (7.8)	458 (29.0)	1831	5.8	224 (12.2)	217 (11.9)
West Midlands	1486	18.1	115 (7.7)	454 (30.6)	1700	5.8	237 (13.9)	215 (12.6)
East Anglia	674	15.1	33 (4.9)	174 (25.8)	795	5.5	101 (12.7)	96 (12.1)
Oxford	797	17.8	44 (5.5)	247 (31.0)	919	6.7	73 (7.9)	138 (15.0)
North West Thames	1069	17.1	111 (10.4)	305 (28.5)	1204	5.5	178 (14.8)	134 (11.1)
North East Thames	1071	14.3	115 (10.7)	252 (23.5)	1226	5.1	241 (19.7)	120 (9.8)
South East Thames	1050	17.6	75 (7.1)	279 (26.6)	1311	6.6	178 (13.6)	198 (15.1)
South West Thames	981	16.3	68 (6.9)	272 (27.7)	1152	6.5	117 (10.2)	198 (17.2)
Wessex	979	16.0	38 (3.9)	255 (26.0)	1143	5.6	107 (9.4)	135 (11.8)
South Western	1027	15.4	68 (6.6)	246 (24.0)	1266	6.5	127 (10.0)	188 (14.8)

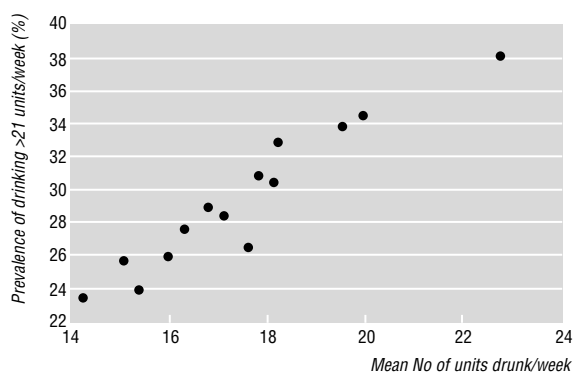


Fig 1 Relation between mean alcohol consumption and prevalence of drinking more than 21 units a week in men across 14 regions in England

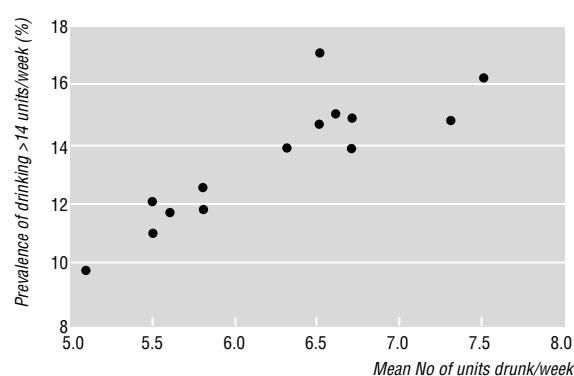


Fig 2 Relation between mean alcohol consumption and prevalence of drinking more than 14 units a week in women across 14 regions in England

Results

Table 1 shows the number of respondents, mean consumption, prevalence of abstinence, and prevalence of drinking above 21 and 14 units for men and women respectively for the 14 regions from the north to the south of England. There was greater variation in the mean consumption and the prevalence of heavy drinking between regions among men than among women.

There was a strong positive association between mean regional consumption and the prevalence of heavy drinking (figs 1 and 2), and this was found with all three definitions of heavy drinking (table 2). Unsur-

Table 2 Association of mean alcohol consumption in total population and in population excluding heavy drinkers with prevalence of heavy drinking across 14 English regions

Definition of heavy drinking	Total population		Heavy drinkers excluded	
	Correlation coefficient	Regression coefficient (95% CI)*	Correlation coefficient	Regression coefficient (95% CI)*
Men (units/week (prevalence))				
>43† (10%)	0.90 (P<0.0001)	0.9 (0.7 to 1.2)	0.68 (P=0.008)	1.3 (0.4 to 2.2)
>28 (21%)	0.90 (P<0.0001)	1.4 (1.0 to 1.9)	0.55 (P=0.04)	1.3 (0.1 to 2.5)
>21 (30%)	0.95 (P<0.0001)	2.1 (1.6 to 2.6)	0.75 (P=0.002)	6.3 (2.8 to 9.8)
Women (units/week (prevalence))				
>21 (7%)	0.90 (P<0.0001)	1.6 (1.1 to 2.1)	0.63 (P=0.02)	2.0 (0.4 to 3.5)
>17† (10%)	0.92 (P<0.0001)	1.9 (1.4 to 2.4)	0.76 (P=0.002)	3.4 (1.6 to 5.2)
>14 (14%)	0.88 (P<0.0001)	2.6 (1.7 to 3.5)	0.62 (P=0.02)	4.8 (0.9 to 8.7)

*Absolute difference in prevalence of heavy drinking (%) with 1 unit/week difference in mean consumption.
†90th Centile of consumption for each sex.

Table 3 Association between median alcohol consumption and heavy drinking across 14 English regions

Definition of heavy drinking	Correlation coefficient	Regression coefficient (95% CI)*
Men (units/week (prevalence))		
>43† (10%)	0.79 (P=0.0008)	0.8 (0.4 to 1.2)
>28 (21%)	0.84 (P=0.0002)	1.3 (0.8 to 1.8)
>21 (30%)	0.96 (P<0.0001)	2.1 (1.7 to 2.4)
Women (units/week (prevalence))		
>21 (7%)	0.72 (P=0.004)	1.3 (0.5 to 2.2)
>17† (10%)	0.74 (P=0.003)	1.6 (0.7 to 2.5)
>14 (14%)	0.80 (P=0.0007)	2.5 (1.3 to 3.7)

*Absolute difference in prevalence of heavy drinking (%) with 1 unit/week difference in median consumption.

†90th Centile of consumption for each sex.

prisingly, the association was weakened when heavy drinkers were excluded from calculation of mean consumption, but it still remained strong. The association was similar for men and women (table 2). The associations were of similar magnitude when the analysis was restricted to those aged under 65 years and when abstainers were excluded.

Median consumption was strongly associated with the prevalence of heavy drinking across regions (table 3). As the proportion of abstainers could influence this association, we repeated the analysis excluding them. The association between median consumption in drinkers and the prevalence of heavy drinking was of a similar size to that in the whole population. For example, when heavy drinking was defined as above the 90th centile the correlation coefficients with median consumption in drinkers were 0.90 and 0.75 for men and women respectively.

On the basis of these data, a difference in the mean consumption of alcohol of 1 unit a week among men who did not drink heavily was associated with 1.3% more of the male population drinking above the current sex specific 90th centile or with 6.3% more drinking above 21 units a week (table 2). A similar difference among women who did not drink heavily was associated with 3.4% more women drinking above the sex specific 90th centile.

The association between the prevalence of abstinence in men and women and the mean consumption in drinkers was much weaker ($r=0.08$, $P=0.8$ for men and $r=-0.29$, $P=0.3$ for women). The association between the median consumption in drinkers and the prevalence of abstinence was of similar size ($r=-0.05$, $P=0.9$ among men and $r=-0.35$, $P=0.2$ in women).

The prevalence of problem drinking and physical dependence as defined by the CAGE questionnaire increased with drinking level (table 4). The prevalence of problem drinking was 3.7% among men and 2.3% among women drinking less than 21 and 14 units per week respectively. Regionally, the correlation between problem drinking and prevalence of drinking above the 90th centile for the total population was stronger among men ($r=0.65$, $P=0.01$) than women ($r=0.45$, $P=0.1$). Among those who drank the correlation between problem drinking and prevalence of drinking above the 90th centile was much higher for men ($r=0.64$, $P=0.01$) than women ($r=0.24$, $P=0.4$). Among women drinkers a higher correlation was seen for the association between the regional prevalence of regional heavy drinking and the physical dependence

Table 4 Prevalence (%) of problem drinking and physical dependence defined by CAGE questionnaire by drinking level among drinkers

Definition of heavy drinking	Problem drinking	Physical dependence
Men (units/week)		
>43*	32	25
>28	23	17
>21	19	15
Women (units/week)		
>21	23	15
>17*	20	12
>14	16	10

*90th Centile of consumption for each sex.

score ($r=0.49$, $P=0.07$ for women and $r=0.54$, $P=0.05$ for men).

A moderately strong association among men and women was found between the mean and median consumption among drinkers and the proportion of drinkers with CAGE defined problem drinking (table 5). Among women the score for physical dependency showed a stronger association than the score for problem drinking.

Discussion

Our analysis confirms that the prevalence of heavy drinking is strongly associated with the mean and median consumption of the population across England and also shows that this is true for women and men. This builds on previous evidence supporting a dynamic relation between average consumption and heavy drinking and dismisses the idea that this relation does not exist within the United Kingdom. Regions where the average level of consumption is lower have fewer heavy drinkers—that is, there is a corresponding downward shift of the distribution. Among men, for example, the highest prevalence of drinking more than 21 units a week was in the Northern region (38.5%), where mean consumption was 22.7 units a week, and the lowest prevalence was in the North East Thames region (23.5%), where the mean was 14.3 units a week.

Previous analyses have tackled the problem of inbuilt correlation by repeating analysis with heavy drinkers excluded from the mean value.³ We took this further by examining the association of the median consumption with the prevalence of heavy drinking. Median consumption does not have an inbuilt correlation with the prevalence of heavy drinking. We found associations between median consumption and heavy drinking that were as strong as those for mean consumption.

Similarly, CAGE scores did not contribute to mean consumption and therefore any associations found cannot be due to an inbuilt correlation with heavy drinking. The prevalence of CAGE defined problem drinking was associated with both mean and median consumption in drinkers. Among men our analysis shows that variation between regions in mean or median consumption among drinkers is associated with variation in the prevalence of problem drinking.

Among women CAGE defined physical dependence showed a stronger association with average consumption and heavy drinking than did CAGE defined problem drinking. Our data suggest that CAGE data among women should be interpreted with

caution; relevantly, the early validation studies of the CAGE questionnaire were largely in male patients.¹⁴

Implications for alcohol policy

We emphasise that our findings do not imply an inevitable relation between average consumption and prevalence of heavy drinking. An increase in mean consumption could result from a few abstainers taking a small amount of alcohol or from heavy drinkers increasing the amount they drink, without any change in the prevalence of heavy drinking. Neither do our findings rule out the possibility that measures aimed at the drinking practices of specific subgroups of the population rather than the general population might change the practices of people in a specific part of the distribution. For example, advice on the adverse consequences of abstinence might change the practice of abstainers; indeed, such advice was given by the Interdepartmental Working Party.¹ However, as noted above, when abstainers are excluded from the analysis the remaining variation both in median and mean consumption in moderate drinkers is strongly associated with variation in the prevalence of heavy drinking. Thus many factors determine a person's or population subgroup's alcohol consumption, but our analysis strongly supports the thesis that some social mechanisms have a detectable influence on drinking patterns in the collective population and that these have implications for public health.

The Interdepartmental Working Group's recommendation of an increase in sensible drinking benchmarks aims to inform the public that higher consumptions than previously recommended are safe and to encourage small amounts of regular drinking as opposed to bingeing.¹ However, it assumes that heavy drinkers are indifferent to the acceptability of drinking in their culture and that an upward shift in consumption among moderate drinkers, which might result from increasing the benchmark for so called sensible drinking, is harmless. Our analysis suggests that this is not the case and that higher average consumption among moderate drinkers is associated with higher rates of heavy drinking and problem drinking. A separate issue is of course that, overall, the greatest burden of alcohol related problems is among the large group of moderate drinkers at low risk rather than the smaller number of people at high risk.

A much weaker association was found between the prevalence of abstinence and mean consumption in

Table 5 Association of mean and median consumption among drinkers with problem drinking and physical dependence defined by CAGE questionnaire

CAGE defined problem (score)	Mean consumption		Median consumption	
	Correlation coefficient	Regression coefficient (95% CI)*	Correlation coefficient	Regression coefficient (95% CI)†
Men				
Problem drinking (≥ 2)	0.53 (P=0.05)	0.3 (0.1 to 0.7)	0.42 (P=0.1)	0.3 (-0.1 to 0.6)
Physical dependence (≥ 1)	0.39 (P=0.20)	0.2 (-0.1 to 0.5)	0.36 (P=0.2)	0.2 (-0.1 to 0.5)
Women				
Problem drinking (≥ 2)	0.42 (P=0.13)	0.5 (-0.2 to 1.2)	0.57 (P=0.03)	0.8 (0.08 to 1.6)
Physical dependence (≥ 1)	0.64 (P=0.01)	0.6 (0.1 to 1.1)	0.67 (P=0.008)	0.9 (0.3 to 1.5)

*Absolute difference in prevalence of problem drinking and physical problems (%) with 1 unit/week difference in mean consumption.

†Absolute difference in prevalence of problem drinking and physical problems (%) with 1 unit/week difference in median consumption.

drinkers, particularly among men. This suggests that the social determinants of abstinence may differ from those that interweave the consumption patterns of heavy and moderate drinkers. Therefore, an increase in mean consumption among drinkers cannot be assumed to result in decreased abstinence. In other words, the adverse consequences of an increase in heavy drinking could not be assumed to be offset by the beneficial effects on cardiovascular disease from a decrease in abstinence.

There are several limitations to this analysis. We examined variations in consumption by regional health authority, so the correlation was based on only 14 areas. This reduced our power to show significant associations, although the large sample size did allow our estimates of both consumption and heavy drinking to be precise. Very heavy drinkers are likely to be underrepresented in population based household surveys which do not include non-household residences.¹⁵ However, this non-response would tend to reduce the power to detect an association between the regional median or mean in moderate drinkers and the prevalence of heavy drinking rather than to a false positive association. A false positive association would result only if the non-response was systematically higher among heavy drinkers in regions with lower mean consumption among moderate drinkers, which is unlikely. Heavy consumers have also been shown in some but not all studies to understate their consumption, and estimates of consumption from surveys are usually less than those expected from sales statistics.¹⁵ In addition, some studies have found that married women underreport consumption if their husband is present, although in general sex differences in validity of reporting are not found.¹⁶ Misclassification of heavy drinkers could give rise to an association between mean consumption and the prevalence of heavy drinking under certain conditions. However, misclassification could not account for the association that we found between the prevalence of heavy drinking and median consumption unless heavy drinkers were misclassified as drinking less than median, which is most unlikely.

Our analysis is based on cross sectional data. Such associations do not necessarily mean that similar changes will be seen with changes in mean consumption over time.¹⁰ This is a valid criticism, but it is countered by other analyses that have shown increases in heavy drinking with increases in mean consumption over time.⁵

Conclusion

The influence of guidelines or benchmarks on drinking behaviour is questionable.¹⁷ However, other policies such as the liberalisation of opening hours or reducing the real cost of alcohol are likely to be more effective in increasing mean consumption. Our data suggest that policies that increase consumption of the general population may lead to an increase in the amount of problem drinking and related problems

Key messages

- Regional mean alcohol consumption of those who do not drink heavily is strongly correlated with the regional prevalence of heavy drinking
- Regional mean consumption is also associated with the regional prevalence of problem drinking as defined by the CAGE questionnaire
- These observations imply that factors increasing mean consumption in light to moderate drinkers are likely to result in an increase in heavy drinking and related problems
- The regional prevalence of abstinence is not strongly associated with regional mean consumption, so any increase in problems from heavy drinking resulting from an increase in mean consumption cannot be assumed to be offset by beneficial effects on cardiovascular disease from reduced abstinence

and are therefore not in the interest of the public's health.

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Assessment of the zinc turbidity test and the use of risk factors in detecting asymptomatic hepatitis C virus carriers: population based study

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Early detection of carriers of hepatitis C virus, who are at risk of the long term sequelae of the infection, is necessary to provide comprehensive medical benefits such as education, follow up, and treatment.¹ However, alanine aminotransferase concentration, even when measured several times, is a poor serum marker for detecting carriers because concentrations are often normal.² Screening a healthy population by determining antibodies or hepatitis C virus RNA is not feasible. To target a population suspected of harbouring hepatitis C virus infection for further examination, we evaluated other biochemical tests as well as the use of risk factors for hepatitis C infection.

Subjects, methods, and results

Our 281 subjects, aged 30-82 (mean 55) years, (124 men) represented 43% of all residents who had health checkups in 1993 in a town with a high mortality from liver diseases. We assessed alanine aminotransferase (normal ≤ 35 IU/l), aspartate aminotransferase (≤ 40 IU/l), γ -glutamyl transpeptidase (≤ 50 IU/l), zinc turbidity (≤ 12.0 Kunkel), second generation antibody to hepatitis C virus (enzyme immunoassay; positive rate 27.0%), hepatitis B surface antigen (positive rate 1.8%), and risk factors for hepatitis C virus infection. Hepatitis C virus RNA was measured in 61 seropositive subjects. From four biochemical tests and eight risk factors, logistic regression (SAS-PC) was used to determine predictors for the infection.

As predictors of seropositivity, abnormal values in the zinc turbidity test (95% confidence interval 3.4 to 38); a history of jaundice of an unknown aetiology (1.8 to 11), blood transfusion (1.2 to 12), or acupuncture (0.9 to 4.0); and abnormal concentrations of alanine aminotransferase (0.6 to 7.6) were selected. Table 1 shows the predictability of seropositivity with different combinations of predictors. To simplify prediction, each predictor was assigned the same weight. The zinc turbidity test had higher sensitivity and specificity than alanine aminotransferase; together they had a higher positive predictive value than alanine aminotransferase alone. When the risk factors were considered, the specificities were substantially decreased. All 19 seropositive subjects with abnormal zinc turbidity had hepatitis C virus RNA (10^5 - 10^7 copies/ml).

Comment

The difficulty in evaluating results of the zinc turbidity test has been the low specificity for liver diseases since the level reflects the overall fluctuations in several serum protein concentrations.³ We found that the zinc turbidity test was highly specific to positivity for antibodies to hepatitis C virus—possibly because its results, unlike other those of biochemical tests, are normal in fatty liver and alcoholic liver disease, which are often observed in healthy subjects undergoing routine physical examinations. Furthermore, several diseases which cause raised values on the zinc turbidity test, such as hepatitis B, connective tissue diseases, and myelomas,³ are less common than hepatitis C in healthy people in Japan. When the zinc turbidity test is used in other countries, the prevalence of diseases affecting its results, racial variations in the normal value, and reproducibility among laboratories should be considered.

In selected geographical areas, the zinc turbidity test helps detect carriers of hepatitis C virus who may have persistent liver damage despite having normal aminotransferase concentrations. These carriers should be given an opportunity for further clinical evaluation, even though their prognosis may differ from that of carriers with abnormal aminotransferase concentrations.⁴ Like the alanine aminotransferase concentration, the zinc turbidity test can fail to detect asymptomatic carriers. Because of the many false positive results, risk factors seem to be more useful as educational preventive tools than as ways to target high risk populations.

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Table 1 Predictability of positivity for antibodies to hepatitis C virus. Values* are percentages of 281 subjects (SD)

Predictive criteria for seropositivity	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Alanine aminotransferase >35 IU/l	20.1 (5.2)	96.9 (1.3)	66.9 (11.1)	80.0 (2.6)
Zinc turbidity test >12.0 Kunkel	36.6 (6.3)	98.0 (1.0)	84.6 (7.3)	83.6 (2.5)
Both of the above	41.8 (6.1)	94.9 (1.5)	71.4 (7.8)	84.3 (2.4)
Both plus history of jaundice	56.8 (6.2)	88.4 (2.3)	59.4 (6.4)	87.2 (2.3)
Both plus history of jaundice and blood transfusion	61.8 (6.4)	82.4 (2.8)	51.5 (5.8)	87.6 (2.4)
Both plus history of jaundice and blood transfusion and acupuncture	83.4 (4.9)	60.5 (3.5)	39.0 (4.3)	92.2 (2.3)

*Not including 23 subjects with missing values. Values were obtained by the bootstrap method based on 1000 trials.