

Migraine, vascular risk, and cardiovascular events in women: prospective cohort study

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EDITORIAL by Lipton and Derby

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ABSTRACT

Objectives To evaluate whether the association between migraine with aura and increased risk of cardiovascular disease is modified by vascular risk groups as measured by the Framingham risk score for coronary heart disease.

Design Prospective cohort study.

Setting Women's health study, United States.

Participants 27 519 women who were free from cardiovascular disease at baseline with available information on the Framingham risk score and migraine status.

Main outcome measures Time to major cardiovascular disease event (non-fatal myocardial infarction, non-fatal ischaemic stroke, death from ischaemic cardiovascular disease), myocardial infarction, and ischaemic stroke.

Results At baseline, 3577 (13.0%) women reported active migraine, of whom 1418 (39.6%) reported migraine with aura. During 11.9 years of follow-up, there were 697 cardiovascular disease events. We stratified participants based on 10 year risk of coronary heart disease estimated from the Framingham risk score ($\leq 1\%$, 2-4%, 5-9%, and $\geq 10\%$). Compared with women without migraine, the age adjusted hazard ratios in women with active migraine with aura were 1.93 (95% confidence interval 1.45 to 2.56) for major cardiovascular disease, 1.80 (1.16 to 2.79) for ischaemic stroke, and 1.94 (1.27 to 2.95) for myocardial infarction. When stratified by Framingham risk score, the association between migraine with aura and major cardiovascular disease was strongest in the lowest risk score group. There was a diametric association pattern for ischaemic stroke and myocardial infarction. Compared with women without migraine, the age adjusted hazard ratios in women who reported migraine with aura in the lowest Framingham risk score group were 3.88 (1.87 to 8.08) for ischaemic stroke and 1.29 (0.40 to 4.21) for myocardial infarction. Hazard ratios in women with migraine with aura in the highest Framingham risk score group were 1.00 (0.24 to 4.14) for ischaemic stroke and 3.34 (1.50 to 7.46) for myocardial infarction. Women with migraine without aura were not at increased risk of ischaemic stroke or myocardial infarction in any of the Framingham risk score groups.

Conclusion The association between migraine with aura and cardiovascular disease varies by vascular risk status.

Information on history of migraine and vascular risk status might help to identify women at increased risk for specific future cardiovascular disease events.

Trial registration Clinical trials NCT00000479.

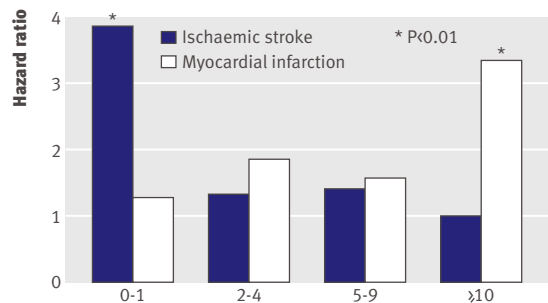
INTRODUCTION

Migraine with aura is associated with an increased risk of ischaemic stroke,¹⁻⁴ migraine angina^{5,6} and other ischaemic vascular events, including myocardial infarction.^{7,8} It remains unclear which mechanisms link migraine with vascular events and whether the biological mechanisms leading to ischaemic stroke differ from the mechanisms leading to myocardial infarction.

A potential association between migraine and cardiovascular disease that depends on the underlying vascular risk status might help clinicians identify individuals at increased risk of future cardiovascular disease events. We evaluated whether the association between migraine with aura and overall and specific cardiovascular disease events differed according to vascular risk status, as measured by the Framingham risk score.

METHODS

Study population—We carried out a prospective cohort study among participants in the women's health study, a trial designed to test the benefits and risks of low dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. Methods and results have been described previously.⁹ Briefly, 39 876 US female health professionals aged ≥ 45 at study entry (1992-5) and without a history of cardiovascular disease, cancer, or other major illnesses, were enrolled. Baseline information was self-reported and collected by questionnaire asking about many vascular risk factors and lifestyle variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires. For this analysis, we included follow-up information from study entry to 31 March 2007. As of this date, follow-up was 97% complete. Before randomisation, blood samples were collected from 28 345 participating women and analysed for lipids and inflammatory biomarkers. Cholesterol analyses were performed on 27 939 of the samples.



Framingham estimate of 10 year risk of coronary heart disease (%)

Age adjusted association between migraine with aura and ischaemic stroke and myocardial infarction according to 10 year risk of coronary heart disease estimated by Framingham risk score. Reference group was women without history of migraine

Assessment of migraine—From information of the baseline questionnaire, we categorised women into “no history of migraine” and “any history of migraine.” We also distinguished between “active migraine,” (migraine in the year before), and “prior migraine,” (history of migraine, but none in the year before). Those participants who reported active migraine were asked about migraine specific features and were classified into active migraine with aura and active migraine without aura.

Framingham risk score—We used the Framingham risk score, which predicts the 10 year risk of coronary heart disease, to classify participating women into vascular risk classes.¹⁰ This score assigns points for age, total cholesterol, high density lipoprotein cholesterol, smoking, and systolic blood pressure stratified by treatment for hypertension. The points for each individual component are summed and categorised into groups of 10 year risk of coronary heart disease of $\leq 1\%$ (≤ 12 points), 2-4% (13-16 points), 5-9% (17-19 points), and $\geq 10\%$ (≥ 20 points).

Outcome ascertainment—All participants were followed up for the occurrence of a major ischaemic vascular event, a combined end point defined as the first of any of non-fatal ischaemic stroke, non-fatal myocardial infarction, or ischaemic cardiovascular death. In addition, we evaluated any first myocardial infarction, ischaemic stroke, coronary revascularisation procedure, and angina. Medical records were obtained for all reported cardiovascular end points except angina and reviewed by an end points committee of physicians. See bmj.com.

Statistical analyses—We compared the baseline characteristics of participants, with respect to their migraine status. We used logistic regression models to calculate prevalence odds ratios of the association between migraine and migraine aura status with Framingham risk score groups, adjusting for age. We used age adjusted Cox proportional hazards models to evaluate the association between migraine and migraine aura status with risks of incident cardiovascular disease or angina. We ran stratified analyses on categories of predicted 10 year risk of coronary

heart disease based on Framingham risk score. In addition, we ran stratified analyses of the association between migraine status and the various outcomes for individual components of the Framingham risk score.

RESULTS

Of the 27 519 participants who remained in the study after exclusions, 5074 (18.4%) women reported any history of migraine, and 3577 (13.0%) reported active migraine, of whom 1418 (39.6%) reported migraine aura.

Baseline characteristics according to migraine status are shown on bmj.com. Compared with women without a history of migraine, women with active migraine with aura were younger, less likely to consume alcohol, less likely to exercise regularly, and more likely to currently use hormone therapy after menopause. Women with prior migraine tended to have raised total cholesterol concentration and were more likely to currently smoke cigarettes, have raised systolic blood pressure, and more likely to have a history of hypertension compared with the other migraine groups. Mean concentration of high density lipoprotein cholesterol was higher among women without a history of migraine. Family history of myocardial infarction was equally distributed among the migraine groups.

During a mean of 11.9 years of follow-up (326 547 person years), 697 participants suffered a first major ischaemic cardiovascular disease event, which, taking into account the potential for multiple events in a single individual, included 306 first ischaemic strokes, 301 first myocardial infarctions, and 148 deaths from cardiovascular disease. In addition, 647 underwent coronary revascularisation, and 412 reported angina during follow-up. The risk of major cardiovascular disease increased with increasing Framingham risk score estimated 10 year risk of coronary heart disease. Compared with women with a risk $\leq 1\%$, the age adjusted hazard ratios for major cardiovascular disease were 3.11 (2.46 to 3.93), 6.04 (4.67 to 7.81), and 10.40 (7.76 to 13.94) for women with risks of 2-4%, 5-9%, and $\geq 10\%$, respectively.

Active migraine with aura was associated with about a twofold increased risk of major cardiovascular disease, ischaemic stroke, and myocardial infarction (table). After stratification by Framingham risk score, the pattern of association between active migraine with aura and major cardiovascular disease was U shaped, with the highest estimate in the lowest risk score group. We observed a strikingly different pattern of association for the outcomes of ischaemic stroke and myocardial infarction (table, figure).

When we evaluated the individual components of the Framingham risk score, the association between active migraine with aura and ischaemic stroke was particularly apparent for the younger age groups (45-54 and 55-64), was not apparent among women aged ≥ 65 , and was further increased for women aged 45-49 (5.35, 2.08 to 13.79; $P < 0.001$). With regard to systolic

blood pressure, we found a greater risk of ischaemic stroke for women with low blood pressure, specifically magnified among women with systolic blood pressure <110 mm Hg (5.18, 1.70 to 15.80; $P<0.004$). The associated risk of ischaemic stroke for women with active migraine with aura increased with decreasing total cholesterol concentrations. Women with migraine with aura and cholesterol <4.40 mmol/l had increased risk (4.01, 1.15 to 13.96, $P=0.03$). This pattern was not driven by high density lipoprotein cholesterol. There was a U shaped pattern with regard to smoking, showing increased risk for current smokers and those who had never smoked, which reached significance for those who had never smoked. See bmj.com.

For myocardial infarction the association between active migraine with aura and myocardial infarction was increased in the age groups 45-54 and 55-64. There was no further increased risk when we evaluated the age group 45-49. With regard to systolic blood pressure, we found an increased risk of myocardial infarction for women with active migraine with aura who had values <120 mm Hg and ≥ 140 mm Hg. The associated risk of myocardial infarction was strongest for women with active migraine with aura who had a systolic blood pressure <110 mm Hg (10.00, 2.96 to 33.77; $P<0.001$). The association increased with increasing total cholesterol concentrations. As with

ischaemic stroke, the pattern of association was U shaped across smoking categories.

DISCUSSION

Summary of findings

In this large prospective cohort of women, the association between active migraine with aura and ischaemic stroke was apparent only among women in the lowest Framingham risk score group, while the association with myocardial infarction was apparent only among women in the highest Framingham risk score group. This diametric pattern of association was driven by particularly increased risk of ischaemic stroke among women with active migraine with aura who were young (aged 45-49) and who had low total cholesterol concentrations. In contrast, women with active migraine with aura who had high total cholesterol concentrations had an increased risk of myocardial infarction. The association between migraine with aura and coronary revascularisation procedures was similar to the myocardial infarction finding, while our data suggest a U shaped association between migraine with aura and angina according to Framingham risk score groups (see bmj.com).

Our data add to the growing evidence that migraine is associated with increased risk of vascular events^{2,4,7,8} and that the risk of specific cardiovascular disease outcomes might depend on the presence or absence of

Age adjusted association (hazard ratio) between migraine and cardiovascular disease, stratified by Framingham estimate of 10 year risk of coronary heart disease* in 27 519 women in women's health study

	No history of migraine (n=22 445)†	Active migraine with aura (n=1418)			Active migraine without aura (n=2159)			Prior migraine‡ (n=1497)		
		No of women	HR (95% CI)	P value	No of women	HR (95% CI)	P value	No of women	HR (95% CI)	P value
Major cardiovascular event§ (n=697)										
Overall	557	53	1.93 (1.45 to 2.56)	<0.001	39	1.00 (0.72 to 1.38)	0.98	48	1.23 (0.92 to 1.66)	0.16
Framingham risk group:										
≤1%	80	14	2.69 (1.52 to 4.75)	<0.001	9	1.09 (0.55 to 2.18)	0.80	8	1.72 (0.83 to 3.57)	0.14
2-4%	204	16	1.60 (0.96 to 2.67)	0.07	18	1.22 (0.75 to 1.99)	0.42	11	0.74 (0.40 to 1.36)	0.33
5-9%	169	14	1.80 (1.04 to 3.11)	0.04	9	0.87 (0.45 to 1.71)	0.69	16	1.19 (0.71 to 1.98)	0.51
≥10%	104	9	1.93 (0.97 to 3.82)	0.06	3	0.52 (0.17 to 1.66)	0.27	13	1.32 (0.74 to 2.35)	0.35
Ischaemic stroke (n=306)										
Overall	251	22	1.80 (1.16 to 2.79)	0.008	17	0.99 (0.60 to 1.62)	0.97	16	0.91 (0.55 to 1.50)	0.70
Framingham risk group:										
≤1%	36	9	3.88 (1.87 to 8.08)	<0.001	4	1.09 (0.39 to 3.07)	0.87	3	1.44 (0.44 to 4.66)	0.55
2-4%	94	6	1.34 (0.59 to 3.07)	0.48	9	1.39 (0.70 to 2.77)	0.35	3	0.44 (0.14 to 1.38)	0.16
5-9%	77	5	1.41 (0.57 to 3.51)	0.46	2	0.43 (0.11 to 1.75)	0.24	8	1.30 (0.63 to 2.70)	0.48
≥10%	44	2	1.00 (0.24 to 4.14)	0.99	2	0.96 (0.23 to 4.00)	0.95	2	0.49 (0.12 to 2.02)	0.32
Myocardial infarction (n=301)										
Overall	240	24	1.94 (1.27 to 2.95)	0.002	17	0.95 (0.58 to 1.56)	0.85	20	1.20 (0.76 to 1.89)	0.44
Framingham risk group:										
≤1%	35	3	1.29 (0.40 to 4.21)	0.67	4	1.10 (0.39 to 3.09)	0.86	3	1.48 (0.45 to 4.80)	0.52
2-4%	83	8	1.87 (0.90 to 3.88)	0.09	9	1.41 (0.71 to 2.83)	0.33	5	0.83 (0.34 to 2.04)	0.68
5-9%	79	6	1.58 (0.69 to 3.65)	0.28	3	0.60 (0.19 to 1.92)	0.39	6	0.94 (0.41 to 2.16)	0.89
≥10%	43	7	3.34 (1.50 to 7.46)	0.003	1	0.35 (0.05 to 2.54)	0.30	6	1.36 (0.58 to 3.20)	0.48

*Women in each risk group: 14 862 in ≤1%; 8399 in 2-4%; 3167 in 5-9%; 1091 in ≥10%.

†Hazard ratio=1.

‡History of migraine but no active migraine in year before completion of baseline questionnaire.

§Defined as first of any of: non-fatal ischaemic stroke, non-fatal myocardial infarction, or death from ischaemic cardiovascular cause.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Migraine with aura is associated with increased risk of ischaemic stroke and other ischaemic vascular events

Migraine with aura is also associated with an unfavourable vascular risk profile as measured by the Framingham risk score for coronary heart disease

WHAT THIS STUDY ADDS

Migraine with aura is only associated with increased risk of ischaemic stroke among women with low vascular risk scores, while migraine with aura is only associated with increased risk of myocardial infarction among women with high vascular risk scores

Information on history of migraine and vascular risk status might help to identify women at increased risk for specific future cardiovascular disease events

vascular risk factors.¹⁴ Our data imply that among patients with migraine, cardiovascular risk factors should be more carefully sought and controlled.

Potential biological mechanisms

Recent studies on the pathophysiology of migraine suggest that migraine can also be viewed in part as a systemic disorder that is affecting the vasculature and migraineurs might have reduced number and functions of endothelial progenitor cells, a surrogate for marker for impaired vascular function.¹¹ Even in the absence of vascular risk factors, people with migraine have decreased cerebral¹² and peripheral vascular resistance¹³ and increased likelihood of retinal microvascular signs,¹⁴ hypercoagulability,¹⁵ and inflammation.¹⁶ Moreover, the altered vascular reactivity is already present among young patients with a recent onset of migraine (mean age 24.6).¹³

It is plausible that the biological mechanisms by which migraine with aura results in ischaemic vascular events in the brain require a vasculature not altered by atherosclerosis but might involve microvascular changes.

The effect of migraine with aura on the coronary arteries might involve two mechanisms, one involving a vasculature not altered by atherosclerosis leading to angina and one involving a vasculature impaired by atherosclerosis leading to angina and myocardial infarction. Moreover, as women who reported a history of migraine but not active migraine at baseline had a stronger association with high Framingham risk score and are also more likely to have increased levels of biomarkers of cardiovascular disease,¹⁷ we suggest that an impaired vasculature might be involved in the declining one year prevalence of migraine in older age groups. Further research is needed, however, to evaluate this further.

Strengths and weaknesses of study

Strengths include the prospective design, large number of participants and outcome events, long follow-up and

participation rate, standardised evaluation of migraine and cardiovascular disease risk factors, confirmed cardiovascular disease events by an endpoints committee of physicians, and the homogeneous nature of the cohort, which could reduce confounding.

Several limitations should be also considered. Firstly, migraine and migraine aura status were self reported leading to potential misclassification. Secondly, we had no detailed information on use of specific drugs for migraine that might be associated with ischaemic events. Thirdly, despite the overall high number of outcome events, this number was small when we stratified by migraine and Framingham risk score group status. Fourthly, our stratified analyses are adjusted only for age and not for other major cardiovascular disease risk factors. We have previously shown, however, that the association between migraine with aura and cardiovascular disease in this cohort is independent of major risk factors for cardiovascular disease.⁷ Residual confounding remains a potential alternative explanation as our data are observational. Finally, participants in the women's health study were all health professionals age ≥ 45 and mostly white, thus generalisability might be limited.

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Competing interests: TK has received funding from the National Institutes of Health, Bayer AG, McNeil Consumer and Specialty Pharmaceuticals, and Wyeth Consumer Healthcare; he is a consultant to i3 Drug Safety, and received an honorarium from Organon for contributing to an expert panel. MS has received funding from the Deutsche Forschungsgemeinschaft and an unrestricted research grant from Merck, Sharp and Dohme. GL has received funding from the National Institutes of Health and received honorariums from Pfizer and Lilly Pharmaceutical for speaking engagements in 2003. JMG has received funding and support from National Institutes of Health, BASF, DSM Pharmaceuticals, Wyeth Pharmaceuticals, McNeil Consumer Products and Pliva; received honorariums from Bayer and Pfizer for speaking engagements, and is a consultant for Bayer, McNeil Consumer Products, Wyeth Pharmaceuticals, Merck, Nutraquest, and GlaxoSmithKline. JEB has received funding and support from the National Institutes of Health and Dow Corning Corporation; research support from Bayer Health Care and the Natural Source Vitamin E Association; and an honorarium from Bayer for speaking engagements.

Ethical approval: Institutional review board of Brigham and Women's Hospital, Boston, MA USA.

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Clomifene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: pragmatic randomised controlled trial

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ABSTRACT

Objective To compare the effectiveness of clomifene citrate and unstimulated intrauterine insemination with expectant management for the treatment of unexplained infertility.

Design Three arm parallel group, pragmatic randomised controlled trial.

Setting Four teaching hospitals and a district general hospital in Scotland.

Participants Couples with infertility for over two years, confirmed ovulation, patent fallopian tubes, and motile sperm.

Intervention Expectant management, oral clomifene citrate, and unstimulated intrauterine insemination.

Main outcome measures The primary outcome was live birth. Secondary outcome measures included clinical pregnancy, multiple pregnancy, miscarriage, and acceptability.

Results 580 women were randomised to expectant management (n=193), oral clomifene citrate (n=194), or unstimulated intrauterine insemination (n=193) for six months. The three randomised groups were comparable in terms of age, body mass index, duration of infertility, sperm concentration, and motility. Live birth rates were 32/193 (17%), 26/192 (14%), and 43/191 (23%), respectively. Compared with expectant management, the odds ratio for a live birth was 0.79 (95% confidence interval 0.45 to 1.38) after clomifene citrate and 1.46 (0.88 to 2.43) after unstimulated intrauterine insemination. More women randomised to clomifene citrate (159/170, 94%) and unstimulated intrauterine insemination (155/162, 96%)

found the process of treatment acceptable than those randomised to expectant management (123/153, 80%) (P=0.001 and P<0.001, respectively).

Conclusion In couples with unexplained infertility existing treatments such as empirical clomifene and unstimulated intrauterine insemination are unlikely to offer superior live birth rates compared with expectant management.

Trial registration ISRCT No: 71762042

INTRODUCTION

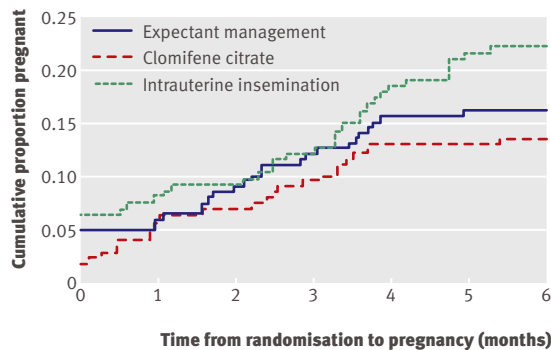
Infertility affects one in seven couples¹ and is described as unexplained when standard investigations (semen analysis, tubal patency tests, and assessment of ovulation) fail to find any abnormalities. Unexplained infertility affects a quarter of infertile couples,¹ some of whom have a reasonable chance of spontaneous live birth.² Expectant management, however, is not a popular option, and several empirical interventions have been used for many years without rigorous prior evaluation. Commonly used first line treatments for unexplained infertility include clomifene citrate and intrauterine insemination.³⁻⁵

We compared the clinical effectiveness and cost of these commonly used treatments against expectant management. We focus here on clinical outcomes.

METHODS

Study design

The study was a three arm, parallel group, pragmatic randomised controlled trial. We recruited patients



Time to pregnancy leading to live birth in groups allocated to clomifene citrate, expectant management, or unstimulated intrauterine insemination. For women with live birth, time to event was defined as number of months between randomisation and estimated date of last menstrual period; women without live birth were censored at end of their follow-up

from five hospitals in Scotland. Inclusion criteria were at least two years of infertility, bilateral tubal patency, ovulation, and normal semen variables. We also included couples with minimum sperm motility of 20% or minimal endometriosis (rAFS stage 1).

Randomisation was carried out with a remote telephone system. The minimisation algorithm balanced allocation of treatment by maternal age, parity, and duration of subfertility, and women were stratified by centre.

Expectant management—This involved six months during which no clinic visits or medical interventions were scheduled. Couples were given general advice regarding the need for regular intercourse, but no specific measures such as basal temperature charts or luteinising hormone kits were recommended.

Clomifene citrate—Women randomised to clomifene citrate received an oral dose of 50 mg between days two and six of each treatment cycle. Couples were advised to have intercourse on days 12-18 of the cycle. If three or more ovarian follicles were detected by scan in the first cycle, the cycle was cancelled and the couple were advised to avoid intercourse. In the next cycle, women who were overstimulated on the first cycle started on a reduced dose of clomifene (25 mg).

Intrauterine insemination—Women were asked to monitor mid-morning urinary luteinising hormone concentrations from day 12 of their cycle using

Clearview (Unipath, Bedford). A single insemination was performed 20-30 hours after an endogenous surge was detected. Couples were advised to avoid intercourse from day 12 of the cycle until the day of insemination. (For details see bmj.com.)

Outcomes

The primary outcome was live birth per woman. Secondary outcomes included clinical pregnancy rate per woman, multiple pregnancy rate, acceptability, adverse events, anxiety, and depression.

Research nurses completed structured records of clinical and procedural details. We used questionnaires completed by women at randomisation and at six months to collect data on acceptability of treatment, side effects, anxiety, and depression. Anxiety and depression were measured with the hospital anxiety and depression scale, with scores of 11 or more suggestive of the relevant mood disorder.⁶ Women who were pregnant at six months after randomisation were followed up to obtain data on delivery.

Statistical analysis

We designed this trial to test two primary comparisons: expectant management versus clomifene citrate and expectant management versus unstimulated intrauterine insemination. Allowing for a 10% loss to follow-up, we estimated that we needed 190 women in each group to show a clinically meaningful improvement in live birth outcomes (from 10% to 22%; odds ratio 2.5) for expectant management versus either clomifene or intrauterine insemination with 80% power and in excess of 95% power to detect a difference in live birth rates of 20% (10% to 30%; odds ratio 4) between expectant management and unstimulated intrauterine insemination at the 5% level of significance.

If both active treatments were found to be more effective than expectant management, we anticipated having over 85% power at the 5% level of significance to detect an absolute difference of 15% (15% to 30%) in live birth rates between the active treatment groups.

We used intention to treat analyses throughout, with a secondary per protocol analysis conducted on live birth rates only. We analysed categorical variables with χ^2 tests, used logistic regression models to

Table 1 | Analysis of live birth for expectant management compared with clomifene citrate or unstimulated intrauterine insemination

Analysis	No (%) in expectant management group	Clomifene citrate v expectant management			Intrauterine insemination v expectant management		
		No (%)	OR (95% CI), P value		No (%)	OR (95% CI), P value	
			Crude	Adjusted*		Crude	Adjusted*
Intention to treat	32/193 (17)	26/192 (14)	0.79 (0.45 to 1.38), 0.49	0.80 (0.45 to 1.42), 0.45	43/191 (23)	1.46 (0.88 to 2.43), 0.18	1.53 (0.91 to 2.56), 0.11
Per protocol	30/187 (16)	24/175 (14)	0.83 (0.47 to 1.45), 0.64	0.83 (0.46 to 1.50), 0.53	31/167 (19)	1.19 (0.69 to 2.07), 0.63	1.25 (0.71 to 2.18), 0.44

*Adjusted for maternal age, parity, duration of infertility, and recruitment centre.

adjust for maternal age, parity, duration of infertility, and recruitment centre, and calculated odds ratios with confidence intervals. We initially compared time to pregnancy leading to a live birth with log rank tests, then used Cox proportional hazards models to make adjustments. Interaction tests for subgroup analyses (planned a priori) were obtained with logistic regression modelling live birth per woman.

For a full description of the methods see bmj.com.

RESULTS

A total of 580 couples were recruited between September 2001 and September 2005. The three randomised groups (expectant management, clomifene citrate, and unstimulated intrauterine insemination) were comparable in terms of women's and men's age, body mass index, semen variables, and proportion of couples with primary infertility. The median duration of infertility was 30 months in each of the randomised groups.

Active treatments

Of the 194 women randomised to clomifene citrate, 93 (48%) women received six completed cycles of clomifene citrate and 18 (9%) received none over the six month trial period. During the trial period, 37/193 (19%) women randomised to unstimulated intrauterine insemination received six completed cycles of intrauterine insemination and 26 (13%) received none.

Live birth

Live birth rates in the three randomised groups were 32/193 (17%) for expectant management, 26/192 (14%)

for clomifene citrate, and 43/191 (23%) for unstimulated intrauterine insemination (table 1). Three women (2%) in the clomifene citrate group and 14 (7%) in the intrauterine insemination group became pregnant spontaneously and had a live birth.

The number needed to treat for harm with clomifene citrate was 33 (95% confidence interval NNH 10 to ∞ to NNB 24). This indicates that if 33 women were treated with clomifene citrate, one fewer would have a live birth than if they all received expectant management, with the confidence interval indicating the uncertainty of the estimate. The number needed to treat for benefit with unstimulated intrauterine insemination was 17 (NNH 51 to ∞ to NNB 7).

There were no significant differences in the time to pregnancy leading to a live birth with clomifene citrate ($P=0.41$) or unstimulated intrauterine insemination ($P=0.17$) compared with expectant management (figure). Compared with expectant management, the adjusted hazard ratio for the time to a pregnancy leading to a live birth was 0.83 (99% confidence interval 0.42 to 1.63) for clomifene citrate and was 1.40 (0.77 to 2.56) for unstimulated intrauterine insemination.

The subgroup analyses for live birth per woman found no modifiers of the effects of clomifene citrate or unstimulated intrauterine insemination compared with expectant management (table 2).

Secondary outcomes

Detailed results for the other clinical outcomes in the three randomised groups are on bmj.com. Clinical pregnancy rates were comparable between expectant management and clomifene citrate (17% *v* 15%) and

Table 2 | Subgroup analysis of live birth by diagnostic group for expectant management compared with clomifene citrate or unstimulated intrauterine insemination, with crude and adjusted P values*

	No (%) in expectant management group	Clomifene citrate <i>v</i> expectant management			Intrauterine insemination <i>v</i> expectant management		
		No (%)	Crude	Adjusted†	No (%)	Crude	Adjusted†
All	32/193 (17)	26/192 (14)	—	—	43/191 (23)	—	—
Pure unexplained infertility:							
No	6/26 (23)	3/19 (16)	0.73	0.76	5/26 (19)	0.33	0.28
Yes	26/167 (16)	23/173 (13)			38/165 (23)		
Mild male infertility factor:							
No	30/184 (16)	23/181 (13)	0.61	0.53	41/177 (23)	0.39	0.25
Yes	2/9 (22)	3/11 (27)			2/14 (14)		
Mild endometriosis:							
No	28/176 (16)	26/183 (14)	—	—	40/178 (22)	0.62	0.68
Yes	4/17 (24)	0/9			3/13 (23)		
Mild male infertility factor and mild endometriosis:							
No	32/193 (17)	26/191 (14)	—	—	43/190 (23)	—	—
Yes	0/0	0/1			0/1		
Type of infertility:							
Primary	24/135 (18)	19/142 (13)	0.59	0.47	29/132 (22)	0.49	0.39
Secondary	8/58 (14)	7/50 (14)			14/59 (24)		

*For treatment*subgroup interaction term.

†Adjusted for maternal age, parity, duration of infertility, and recruitment centre.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Infertility is unexplained in a quarter of all couples with fertility problems

Clomifene citrate or unstimulated intrauterine insemination, commonly used to treat such couples, are endorsed in the UK by the NICE fertility guideline

Previous evidence based on a number of small randomised trials supports the use of clomifene in unexplained subfertility

WHAT THIS STUDY ADDS

Clomifene citrate or unstimulated intrauterine insemination are unlikely to be more effective than no treatment (expectant management)

expectant management and unstimulated intrauterine insemination (17% *v* 23%). Rates of miscarriage and ectopic pregnancy were also similar in the two comparisons, as were rates of multiple pregnancy. Side effects including abdominal pain, bloating, hot flushes, nausea, and headaches were more common in the clomifene citrate group than in the other groups, affecting about 10-20% of women. Despite this, women on active treatments found the process of treatment more acceptable than those randomised to expectant management. The proportion of women scoring 11 or more on the anxiety or depression subscales at six months was similar across the three groups.

DISCUSSION

Clomifene citrate or unstimulated intrauterine insemination seem to be no more effective than expectant management in couples with unexplained infertility.

Strengths and weaknesses

The trial is strengthened by its pragmatic, multicentre approach and the choice of live birth per woman as its end point. The number of women in the expectant management and clomifene citrate arms exceeded the number randomised in all of the previous clomifene citrate trials pooled together.⁷

The inclusion of cases of mild male factor infertility and minimal endometriosis might have introduced an element of clinical heterogeneity. The presence of these cases in this pragmatic trial, however, can be justified on the grounds that they are managed in the same way as “true” unexplained infertility.⁸ Our choice of clinical protocols for the intervention arms reflects current practice in Scotland and the rest of the UK,⁹ but the results might not be generalisable to other populations and alternative drug regimens. In particular, this trial does not address the issue of a combined approach with clomifene citrate and intrauterine insemination, which should be the focus of future trials.

Interpretation within context of setting and intervention

Our results also show that women with infertility are reassured by active treatment and are less satisfied with an expectant approach. Similar concerns in the past have limited the number of fertility trials with a control arm.² Comparable anxiety and depression scores in the randomised groups suggest that preference for active treatment did not translate into greater mental wellbeing in those randomised to clomifene citrate or intrauterine insemination.

As some women did not receive their randomised treatment, we presented a per protocol analysis of live birth rates, along with the intention to treat analysis. We found that unstimulated intrauterine insemination did not enhance live birth, though the upper limit of the 95% confidence interval for the number needed to treat to benefit was 7, a figure that might be perceived to be clinically worthwhile.

Conclusions

Spontaneous live birth rates in a randomised cohort of women with unexplained infertility do not seem to be enhanced by common first line treatments—clomifene citrate or unstimulated intrauterine insemination. These results challenge current practice, as endorsed by a national guideline in the UK.⁹

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Impact of Stepping Stones on incidence of HIV and HSV-2 and sexual behaviour in rural South Africa: cluster randomised controlled trial

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ABSTRACT

Objective To assess the impact of Stepping Stones, a HIV prevention programme, on incidence of HIV and herpes simplex type 2 (HSV-2) and sexual behaviour.

Design Cluster randomised controlled trial.

Setting 70 villages (clusters) in the Eastern Cape province of South Africa.

Participants 1360 men and 1416 women aged 15-26 years, who were mostly attending schools.

Intervention Stepping Stones, a 50 hour programme, aims to improve sexual health by using participatory learning approaches to build knowledge, risk awareness, and communication skills and to stimulate critical reflection. Villages were randomised to receive either this or a three hour intervention on HIV and safer sex. Interviewers administered questionnaires at baseline and 12 and 24 months and blood was tested for HIV and HSV-2.

Main outcome measures Primary outcome measure: incidence of HIV. Other outcomes: incidence of HSV-2, unwanted pregnancy, reported sexual practices, depression, and substance misuse.

Results There was no evidence that Stepping Stones lowered the incidence of HIV (adjusted incidence rate ratio 0.95, 95% confidence interval 0.67 to 1.35). The programme was associated with a reduction of about 33% in the incidence of HSV-2 (0.67, 0.46 to 0.97; $P=0.036$)—that is, Stepping Stones reduced the number of new HSV-2 infections over a two year period by 34.9 (1.6 to 68.2) per 1000 people exposed. Stepping Stones significantly improved a number of reported risk behaviours in men, with a lower proportion of men reporting perpetration of intimate partner violence across two years of follow-up and less transactional sex and problem drinking at 12 months. In women desired behaviour changes were not reported and those in the Stepping Stones programme reported more transactional sex at 12 months.

Conclusion Stepping Stones did not reduce incidence of HIV but had an impact on several risk factors for HIV— notably, HSV-2 and perpetration of intimate partner violence.

Trial Registration Clinical Trials.gov NCT00332878.

INTRODUCTION

Change in sexual behaviour is the cornerstone of HIV prevention, yet relatively little research and development has been invested in interventions aimed at behaviour change in any setting.¹ School based HIV/

AIDS programmes for young people in sub-Saharan Africa have generally not been rigorously evaluated and are often weakly designed, and evaluations suggest they have little impact on sexual behaviours.² In this respect they are no different from programmes for adolescents in other countries.³

Stepping Stones, a participatory HIV prevention programme that aims to improve sexual health through building stronger, more gender equitable relationships, has been widely used for many years.⁴ It was originally developed for use in Uganda in 1995 and has been used in over 40 countries, adapted for 17 settings (including South Africa in 1998⁵), translated into 13 languages, and used with hundreds of thousands of individuals.⁶ We conducted a trial to assess the impact of Stepping Stones on the incidence of HIV and herpes simplex type 2 virus (HSV-2) and sexual practices among men and women in rural areas in the Eastern Cape province of South Africa.

METHODS

Recruitment and randomisation

In this randomised trial we used a cluster design because the intervention is delivered to groups. The setting was historically a subsistence farming region within a radius of 1.5 hours' drive from the town of Mthatha. The unit of randomisation was a geographically defined area in which we recruited one pair of single sex groups. Details of the study design have been described previously.⁷

The 70 study clusters comprised 64 villages and six townships. There was no blinding and for logistical reasons randomisation was done before village recruitment. In each cluster we recruited about 20 men and 20 women volunteers. Those eligible were aged 16-23 normally resident in the village where they were at school, and mature enough to understand the study and the consent process.

After three weeks of training and two practice groups, 11 facilitators delivered the Stepping Stones intervention. Another four, who were trained for four days, administered the control intervention.

Intervention and implementation

Stepping Stones uses participatory learning approaches, including critical reflection, role play, and drama and draws the everyday reality of participants' lives into the sessions. It is delivered to single sex groups, which are

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Table 1 | Incidence of HIV and HSV-2 according to intervention

	Stepping Stones		Control		P value for homogeneity	Adjusted* incidence rate ratio (95% CI)	P value	Coefficient of variation
	No of events	Rate/100 person years	No of events	Rate/100 person years				
HIV								
Overall	72	3.46	81	4.07	0.56	0.95 (0.67 to 1.35)	0.78	1.02
Women	57	5.65	68	6.95				0.81
Men	15	1.40	13	1.29				1.60
HSV-2								
Overall	57	3.24	75	4.62	0.91	0.67 (0.47 to 0.97)	0.036	1.13
Women	43	5.35	57	7.71				0.93
Men	14	1.46	18	2.04				1.58

*Adjusted for stratum, sex, participant's age, and baseline cluster prevalence of HIV or HSV-2, respectively.

run in parallel, and has 13 three hour long sessions that are complemented by three meetings of male and female peer groups and a final community meeting. The programme spanned about 50 hours and ran for six to eight weeks. The control intervention was a single three hour session on HIV, safer sex, and condoms. The content was taken from Stepping Stones.

We administered questionnaires and collected blood samples before the intervention (baseline) and after about one and two years. A trained nurse counsellor provided counselling before HIV testing to groups of eight to 10 people after they had enrolled for the study, signed consent for the interview, and completed the baseline questionnaire. Participants with positive results were told their CD4 counts and screened for medical problems. They also were referred to local health services and HIV support groups according to a referral algorithm. During the study anti-retroviral drugs became available in the public sector and at this point the consent form was changed to ask participants who had opted not to collect their result if they would like to be told if they tested positive.

Laboratory methods

The primary outcome measure was HIV incidence, determined through blood tests at baseline and at 12 and 24 months. All blood tests were conducted blind to treatment arm. HIV status was assessed with two rapid tests with the World Health Organization's testing algorithm.⁸ We used two glycoprotein G based HSV-2 ELISAs to test for herpes infection, Kalon (Kalon Biological, Aldershot, UK) and HerpeSelect Immunoblot IgG (Focus Technologies, Cypress, CA, USA).

We assessed the impact of the intervention on behaviour and attitudes with a questionnaire administered in Xhosa. Details of the outcome measures, indicators, and assessment are on bmj.com and further details can be found elsewhere.⁷

Data analysis

We followed an intention to treat approach. We stratified the analyses for incidence of HIV and

HSV-2 by sex and carried out a test of homogeneity of treatment effect over the sexes. All other analyses were carried out separately for men and women. For each participant we calculated the person years of exposure as the time from baseline to the last negative result if the person remained negative, or as the total time between any negative tests as well as half the time between the last negative and first positive tests. The primary analysis was carried out by fitting generalised linear mixed models (GLMMs) as advocated by Murray.⁹ Generalised estimating equation (GEE) models were also fitted to test the robustness of the GLMMs. For a detailed description of the methods see bmj.com.

RESULTS

Twelve month follow-up rates for women with known HIV status at baseline were 75.8% and 75.3% for women in the intervention and control arms and 75.1% and 71.8% for men in the intervention and control arms, respectively. At 24 months, 73.1% (intervention) and 76.0% (control) of women with baseline HIV results were retested and 69.5% (intervention) and 69.2% (control) of men were tested again for HIV.

Eighteen participants died during the main study and one committed suicide in the pilot study. Causes of death in the main study were interpersonal violence (six), suicide (three), injuries from traffic incident (two), and a range of natural causes (seven), including AIDS (one). Participants' baseline characteristics were similar (see bmj.com), though those in the control arm were slightly more educated ($P=0.09$ for women, $P=0.08$ for men).

Table 1 shows the results for the comparison of incidence rates of HIV and HSV-2 between the two study arms. After adjustment for stratum, baseline HIV prevalence in the cluster, and age of the respondent, Stepping Stones had little effect on the incidence of HIV. The incidence of HSV-2 was significantly lower in the Stepping Stones arm than the control arm (incidence rate ratio 0.67, 95% confidence interval 0.46 to 0.97, $P=0.036$). This represents a 33% reduction in incidence and translates to 34.9 (1.6 to 68.2) infections

being prevented over a two year period per 1000 people in the programme.

Detailed results of the analysis of the other outcomes for women are on bmj.com. There was no evidence of difference in the expected direction between the two arms in any of these outcomes. Some of the other outcomes for men did show differences in the hypothesised direction (table 2).

DISCUSSION

Participation in the Stepping Stones programme in South Africa did not reduce the incidence of HIV infection among young men and women aged 15-26 but was associated with a reduced incidence of herpes simplex type 2 (HSV-2). There was no evidence of any desired behaviour change in women. There was more transactional sex with a casual partner at 12 months (but not at 24 months) among women in the Stepping Stones arm, and there was a suggestion of more unwanted pregnancies at 24 months. Men in Stepping Stones

reported less transactional sex at 12 months, less perpetration of intimate partner violence (significant at 24 months, suggested at 12 months), less problem drinking at 12 months, and less drug misuse at 24 months. There was a suggestion of change in several other outcomes in men, including fewer partners at 12 months, less likelihood of casual partners, less rape at 12 months, and less depression at 24 months.

Strengths

Few randomised controlled trials in Africa have evaluated behavioural interventions with biological outcomes and none has found clear evidence of effect. Our finding of an impact on HSV-2 infection is important for HIV prevention as Stepping Stones is widely used and HSV-2 is an important cofactor in heterosexual transmission of HIV. Meta-analysis indicates that people with HSV-2 have three times the risk of HIV infection.¹⁰

Table 2 | Results for men: other outcomes at 12 and 24 months

	Stepping Stones		Control		Effect* or adjusted odds ratio (95% CI)	P value	Coefficient of variation
	No of participants	Mean* or proportion	No of participants	Mean* or proportion			
No of partners in past year:							
12 months	531	2.28	500	2.51	-0.0078 (-0.033 to 0.0001)	0.063	0.24
24 months	501	2.15	474	2.39	-0.0045 (-0.023 to 0.0003)	0.12	0.25
Any transactional sex with a casual partner:							
12 months	534	0.036	505	0.075	0.39 (0.17 to 0.92)	0.031	1.72
24 months	504	0.018	479	0.019	1.02 (0.39 to 2.65)	0.97	2.09
≥1 incident of physical or sexual intimate partner violence:							
12 months	534	0.114	505	0.149	0.73 (0.50 to 1.06)	0.099	0.63
24 months	504	0.062	479	0.096	0.62 (0.38 to 1.01)	0.054	0.67
Rape or attempted rape:							
12 months	534	0.092	505	0.123	0.71 (0.47 to 1.06)	0.094	1.86
24 months	501	0.080	473	0.085	0.92 (0.53 to 1.58)	0.76	1.91
Impregnated any woman:							
12 months	534	0.086	505	0.083	1.03 (0.66 to 1.62)	0.89	0.82
24 months	504	0.113	479	0.129	0.88 (0.60 to 1.31)	0.53	0.76
Correct condom use at last sex:							
12 months	513	0.735	483	0.689	1.26 (0.92 to 1.74)	0.16	0.22
24 months	485	0.732	462	0.751	0.88 (0.64 to 1.21)	0.43	0.20
Any casual partner:							
12 months	530	0.549	499	0.601	0.79 (0.59 to 1.05)	0.098	0.28
24 months	501	0.531	473	0.569	0.85 (0.62 to 1.15)	0.29	0.33
Depression:							
12 months	534	0.022	505	0.046	0.45 (0.16 to 1.21)	0.11	2.05
24 months	504	0.028	479	0.050	0.52 (0.24 to 1.13)	0.097	1.49
Problem drinking:							
12 months	534	0.198	505	0.265	0.68 (0.49 to 0.94)	0.021	0.57
24 months	504	0.266	479	0.257	1.10 (0.81 to 1.49)	0.56	0.52
Ever misused drugs:							
12 months	337	0.16	310	0.16	1.07 (0.65 to 1.77)	0.78	0.49
24 months	232	0.065	215	0.12	0.50 (0.23 to 1.11)	0.088	0.47

*For No of partners in past year only.

The impact of the intervention on incident infections of HSV-2 in women suggests that desirable behaviour change occurred in at least some women. The prevalence of herpes is much higher in young men than that of HIV and so it is possible that some women were able to change their behaviour with younger male partners in a way that protected them from acquiring HSV-2. This raises the possibility of Stepping Stones having a positive longer term impact on women's HIV risk beyond the period of observation of the study. Further, we suggest that particular care should be given to how transactional sex is discussed in groups of young women (see [bmj.com](#)).

Stepping Stones is a behavioural intervention that, according to a recent classification of interventions by WHO, is regarded as "gender transformative," in that it seeks to transform gender roles and promote more gender equitable relationships between men and women.¹¹

Our results suggest that it did lead to some change in violent and exploitative behaviour in men. Exposure to intimate partner violence has been identified as an important risk factor for HIV in women¹² and so the reduction in male violence might have a broader impact on HIV in their sexual partners well beyond the study setting. Many of the other changes in men's behaviour were not sustained to 24 months, which points to the need for research to strengthen the intervention (see [bmj.com](#)).

Weaknesses

The trial has several weaknesses that might affect the interpretation of the results. Randomisation occurred before recruitment. No villages declined to participate in the study because of their allocation but some individuals did. In both control and intervention clusters we usually had more volunteers for the study than we were able to include so it was not possible to count how many people dropped out during selection because of the allocation as opposed to other reasons, including the need to restrict recruitment to a maximum of 40 per cluster. We noted, however, that some people (particularly women) who lived far from the schools where the sessions were held thought they could not attend the whole Stepping Stones programme. Some women were not allowed to take part because they had strict parents who expected them home quickly after school. It is possible that those in the Stepping Stones arm were in some ways more motivated. This might have differentially influenced the response to the interventions. It is difficult to know how this would have affected our results and generalisability thereof but the modest results, especially for women, suggest it was unlikely that there was a substantial impact.

The generalisability of the study findings could be influenced by several aspects of the trial design. The scope of our intervention was deliberately constrained by affordability in the design of the evaluation. We thus did not evaluate the model of programme delivery originally intended by Welbourn,⁴ which includes groups of older adult participants and multiple groups within the same village. Having done so might have enhanced the overall impact of the programme. This model reflects the socioecological perspective, which has been advocated in HIV prevention.¹³ We designed the trial to measure the impact of Stepping Stones when delivered in a way that reflected the practices of local organisations that work with such programmes. In so doing, our intention was to give some indication of the likely impact of Stepping Stones outside a trial setting. Any weaknesses in delivery of the intervention were probably no greater than those normally found. Our findings are a measure of the difference in outcomes between the two arms. For ethical reasons we provided a reasonably substantial control intervention that focused on HIV prevention and was taken from the Stepping Stones intervention. We cannot exclude the possibility that it resulted in behaviour change, although given the difficulties researchers face in showing impact from behavioural interventions^{2,3} it would be surprising if the control intervention had a substantial impact.

The assumptions we used in calculating the required sample size for the trial were too optimistic. The effect size used in the sample size calculation was large (50% reduction in HIV incidence) and the anticipated overall incidence of HIV was incorrect. In addition, although we used a larger value for the coefficient of variation between clusters than was used in the Mwanza trial, the value used (0.35) was in fact considerably smaller than the actual value of 1.02. Our stratification of the clusters did not help in reducing the variation in incidence rates between clusters, which shows the practical difficulties of stratifying on surrogate geographical variables. Sample size calculations in future evaluations of behavioural interventions should use a more modest estimate of expected effect size. One positive recommendation from this study, which has been supported by other evaluations of behavioural interventions, is that large sample sizes are required to assess the modest but important reductions in incidence of HIV that might result from behavioural interventions and that necessary funding should be provided.

In the control arm slightly more blood specimens were collected by dried blood spot. Although this method for HIV testing was optimised, previous research has suggested that it might be slightly less sensitive than when serum is used.¹⁴ The impact of any such loss of sensitivity would have been to

WHAT IS ALREADY KNOWN ON THE TOPIC

HIV prevention studies have had mixed results in terms of their impact on sexual behaviour

Most studies have been conducted in Western countries; in sub-Saharan Africa no programme has been shown to reduce sexually transmitted infections

WHAT THIS STUDY ADDS

The Stepping Stones programme did not lower incidence of HIV but did reduce the incidence of herpes simplex type 2 virus and male perpetration of intimate partner violence

Stepping Stones can affect some risk factors for HIV in young men and women

underestimate the true incidence of HIV in the control arm.

There could have been contamination between arms, but serious contamination is unlikely as clusters were geographically separated and the total sample size was small compared with the overall population, so the likelihood of participants forming friendships with people from the other study arm was low. Despite considerable efforts to trace cohort members, about 15% failed to contribute any data to the biological outcomes and a quarter were untraceable at 24 months. Our follow-up rates compare favourably with those of similar trials—for example, Ross et al lost 27% to follow-up.¹⁵ As follow-up rates were similar in the intervention and control arms this is unlikely to have biased the results.

Implications

Some would argue that Stepping Stones did not work because it failed to affect the incidence of HIV. Literature on evaluation of behavioural interventions, however, rarely disregards all other outcomes. We analysed the other biological outcome, incidence of HSV-2, across both years and found a reduction in the intervention arm. Most of the changes suggested in other behaviours were not sustained to two years, as is commonly found with evaluations of behavioural interventions, and we endorse the view that for behaviour change to be meaningful it must be enduring.¹³ In contrast, the impact on perpetration of intimate partner violence seems to have been strengthened over the two years of follow-up. This is a pattern that is recognised in the behavioural science literature¹⁶; it results from people having had an opportunity over time to reflect on their behaviour or for the environment to reinforce behaviours. Both HSV-2 and intimate partner violence are established risk factors for HIV and so the observation that Stepping Stones had an effect is of some interest.

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Contribution of problem drug users' deaths to excess mortality in Scotland: secondary analysis of cohort study

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ABSTRACT

Objectives To examine the “Scottish effect”—namely, the growing divergence between mortality in Scotland and England that is not explained by national differences in levels of deprivation—and, more specifically, to examine the extent to which the Scottish effect is explained by cross national differences in the prevalence of problem drug use. **Design** Secondary analysis of cohort study (the DORIS study).

Participants 1033 Scottish drug users recruited to the cohort study in 33 drug treatment facilities across Scotland in 2001-2 and followed up 33 months later in 2004-5.

Results 38 deaths occurred in the cohort, giving a standardised mortality ratio for the cohort of 1244 (95% credible interval 876 to 1678). Only 22 of the 38 deaths in drug users were classified as drug related deaths. From estimates of the size of the problem drug using populations in both England and Scotland, the contribution of deaths in drug users to national death rates can be estimated: the attributable risk fraction for Scotland is 17.3% (12.3% to 22.8%) and that for England is 11.1% (7.8% to 14.8%). Excluding estimated numbers of deaths in drug users would bring down age standardised mortality at ages 15-54 years from 196 to 162 per 100 000 in Scotland and from 138 to 122 per 100 000 in England; 32.0% (22.3% to 43.0%) of the excess mortality in Scotland is due to drug use.

Conclusion Although problem drug use is a low prevalence risk behaviour, it carries a high mortality; the standardised mortality ratio for Scottish drug users is 12 times as high as for the general population. The higher prevalence of problem drug use in Scotland than in England accounts for a third of Scotland's excess mortality over England. Successful public health efforts to reduce the prevalence of problem drug use in Scotland or deaths in Scottish drug users would have a dramatic impact on overall mortality in Scotland.

INTRODUCTION

Death rates are known to be higher in Scotland than in England and Wales. In recent years, although Scottish death rates have been falling, the relative difference between the nations has increased: mortality was 12% higher in Scotland than in England and Wales in 1981 but 15% higher in 2001.¹ In the past, poorer health in Scotland has been attributed to higher levels of deprivation: if local mortality was adjusted for local Carstairs deprivation scores (based on levels of adult male employment, car ownership, social class composition, and overcrowding), 60% of Scotland's excess

mortality in 1981 was explained by greater relative deprivation.² However, by the 1991 census (and continuing at the 2001 census) deprivation was accounting for less than half of Scotland's excess mortality,^{1,3} and the unaccounted for excess was increasingly marked among the Scottish male population aged 0-44 years.¹ This growing disproportionality has been dubbed the “Scottish effect.” Our purpose here is to posit that a single risk factor—problem drug use—may be responsible for a large part of the observed, deprivation adjusted, cross national differences in rates of premature death.

METHODS

DORIS (drug outcomes research in Scotland) is the largest ever repeat interview study of Scottish drug users, involving following up 1033 problem drug users who started a new treatment episode in 33 drug treatment agencies across Scotland in 2001-2. Of the 1180 problem drug users who were asked to participate, 147 people refused, giving a participation rate of 87.5%.

We matched data between General Register Office for Scotland (GROS) mortality data and those members of the DORIS sample who were lost to follow-up at 33 months. The Vital Events Branch of GROS then established which of the deaths in the DORIS cohort had previously been classified as a drug related death in earlier annual reports.⁴ We also made inquiries with the Office for National Statistics in England about whether the death of a DORIS sample member who had died in England had been included in their equivalent count of drug related deaths.

Estimates can be made of the total number of deaths in drug users (as opposed to drug related deaths) by combining the standardised mortality ratio from the DORIS cohort with prevalence data on problem drug use,^{5,6} which are calculated by using identical population estimation methods in Scotland and England. The contribution of deaths among drug users to overall Scottish and English death rates can be calculated as the attributable risk fraction (ARF) in the formula $ARF = P_{pdu} \frac{(SMR/100 - 1)}{(P_{pdu}(SMR/100 - 1) + 1)}$, where P_{pdu} is the proportion of the population who are problem drug users and SMR is the standardised mortality ratio for that same subpopulation calculated through indirect standardisation to the Scottish population.⁷

We estimated the standardised mortality for the non-drug using population in the two countries and, comparing these rates with the observed rates, estimated the proportion of the excess mortality in Scotland that was attributable to drug use. Mortality data and

Table 1 | Crude death rates in DORIS sample

	Person years	All deaths	Drug related deaths cohort	Crude death rate (95% CI) per 1000 person years	Crude death rate (95% CI) for drug related deaths cohort
Men	1953	27	15	14 (9 to 20)	7 (4 to 13)
Women	864	11	7	13 (6 to 23)	8 (3 to 17)
Total	2817	38	22	13 (10 to 18)	8 (5 to 12)

population data came from the Office for National Statistics and the General Register Office (Scotland).⁸⁻¹⁰

We report posterior means and 95% credible intervals estimated with WinBUGS.¹¹ The credible intervals are ranges of values within which the relevant parameter lies with a probability of 0.95; in this sense, they may be interpreted in a similar manner to confidence intervals.

RESULTS

Deaths in DORIS cohort

Thirty eight deaths occurred in the 1033 DORIS sample members in the 33 month period, of which only just over half (22) were classified by the General Register Office for Scotland/Office for National Statistics as “drug related deaths.” The cause of death of one cohort member remained unascertained. Of the remaining 15 cohort deaths that were not classed as drug related, six were suicides, including three overdoses (of paracetamol, amitriptyline, and colchicine), one was an overdose of “undetermined intent” involving fluoxetine and propranolol, three were due to an “infection associated with drug abuse” (with a fourth due to endocarditis), two were due to assaults, one was due to “alcoholic liver disease,” and one was due to hypothermia/exposure.

Table 1 shows mortality as a crude death rate per 1000 person years, where person years are calculated as the difference between the dates of death and of the initial DORIS interview.

Possible contribution of drug use to Scottish excess mortality

The overall (in men and women) standardised mortality ratio for the DORIS cohort is 1244 (95%

credible interval 876 to 1678), and the overall attributable risk fraction is 17.3% (12.3% to 22.8%) for Scotland and 11.1% (7.8% to 14.8%) for England (table 2). The corresponding prevalences of problem drug use are 1.84% (95% confidence interval 1.84% to 2.01%) for Scotland and 1.07% (1.06% to 1.11%) for England. Exclusion of the estimated deaths in drug users resulted in falls in the standardised mortality from 196 per 100 000 to 162 (95% credible interval 150 to 173) per 100 000 in Scotland and from 138 per 100 000 to 122 (117 to 127) per 100 000 in England. This suggests that 32.0% (95% credible interval 22.3% to 43.0%) of the excess Scottish mortality is due to the greater prevalence of problem drug use in Scotland.

DISCUSSION

Our data suggest that one particular risk behaviour, problem drug use, accounts for a third of excess mortality in Scotland compared with England among people aged 15 to 54, supporting Hanlon and colleagues' suggestion that the “Scottish effect” can be explained by higher prevalences of risk behaviours in Scotland than in England within a particular level of deprivation.¹ Note also that a rapid increase in problem drug use (and particularly heroin use) occurred in the 1980s in Scotland,¹² at the very point at which deprivation measures (Carstairs deprivation scores) began to account for less than half of the cross national variance in rates.

Uncertainties and limitations

For Scottish men aged 15-54 (for whom the “Scottish effect” is strongest), deaths in drug users could be accounting for as much as half or as little as a tenth of the excess mortality; however, intervals are narrower when deaths in men and women are combined. The time periods of the different datasets used are not wholly matched; although we have been able to use datasets from contiguous time periods, readers must decide on the windows of applicability of the different datasets.

Eligibility in the DORIS study was simply a matter of starting a new episode of drug treatment; in the English

Table 2 | Proportion of problem drug users, standardised mortality ratios, attributable risk fractions, age standardised mortality, excess mortality, and proportion of excess due to drug use (with 95% credible intervals unless stated otherwise) in England and Scotland, for men and for men and women combined

	Men		Men and women	
	England	Scotland	England	Scotland
Proportion (%) of problem drug users (95% confidence interval)	1.65*	2.69 (2.11 to 4.17)	1.07 (1.06 to 1.11)	1.84 (1.84 to 2.01)
Standardised mortality ratio in population of drug users (DORIS cohort)	†	834 (549 to 1182)	†	1244 (876 to 1678)
Attributable risk fraction (%)	10.7 (6.8 to 15.1)	16.3 (8.8 to 25.5)	11.1 (7.8 to 14.8)	17.3 (12.3 to 22.8)
Age standardised mortality per 100 000	173 (170 to 175)	259 (250 to 267)	138 (136 to 139)	196 (191 to 201)
Excess mortality per 100 000	–	86 (77 to 95)	–	58 (53 to 64)
Age standardised mortality per 100 000, excluding deaths in drug users	154 (146 to 161)	217 (192 to 238)	122 (117 to 127)	162 (150 to 173)
Excess mortality per 100 000, excluding deaths in drug users	–	63 (42 to 80)	–	40 (32 to 47)
Proportion of excess mortality due to drug use (%)	–	27.5 (9.3 to 50.3)	–	32.0 (22.3 to 43.0)

*95% confidence interval not given.

†Assumed to be same as for DORIS cohort.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The excess mortality in Scotland over that in England is greater than can be accounted for by higher deprivation rates

Mortality among drug users is greatly in excess of that in comparable age matched populations

WHAT THIS STUDY ADDS

Only just over half the deaths in the largest ever repeat interview study of Scottish drug users were officially reported as drug related deaths

A third of the “excess” mortality in Scotland can be accounted for by Scotland’s higher prevalence of problem drug use

prevalence study the estimate related to use of opiates, crack/cocaine, or both; in the Scottish prevalence study the estimate related to use of opiates, benzodiazepines, or both. Such differences in definition raise the possibility of numerator-denominator biases in mortality calculations, but the practical importance of definitional differences in this instance is small—for example, although the DORIS sample might have started treatment because of misuse of a range of different substances other than opiates or benzodiazepines, in fact 88% of the sample had used heroin in the three months before recruitment.

The formula used to calculate the attributable risk fraction has been judged to be suitable when no confounding of the exposure-disease association exists,¹³ but we cannot explore the possibility of such confounding in these data. The mortality in DORIS is consistent with that found in studies elsewhere,^{7,14} and the DORIS sample is the largest repeat interview cohort study of Scottish drug users. However, a larger follow-up study of drug users would provide more certain estimates of mortality in drug users.

Implications

Problem drug use is a low prevalence risk behaviour, but it carries a high mortality: mortality in the DORIS sample was 12 times that of the general Scottish population aged 15 to 54. This high mortality is not fully reflected in published reports on “drug related deaths,” as the definition of such deaths is deliberately and properly a restrictive one, limited to deaths due to overdoses of illicit drugs. In the DORIS sample, only just over half the deaths that occurred among drug users were classed as drug related deaths. It follows that deaths in problem drug users are a potentially important contributor to national and local mortality.^{15,16} The identification of an important role for problem drug use in understanding excess mortality does not, of course, decrease the importance of the link between socioeconomic deprivation and poor health.

Successful public health initiatives to reduce the prevalence of problem drug use or to reduce deaths among drug users would have a strong impact on overall mortality in both Scotland and England.

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Ethical approval: Ethical oversight of the DORIS study was exercised by the Scottish Multi-Centre Research Ethics Committee, which also granted permission to apply to the General Register Office for Scotland (GROS) to establish which deaths had occurred among members of the cohort who had been lost to follow-up at 33 months. The GROS application was approved by the medical adviser to the registrar general and by the Privacy Advisory Committee.

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