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Influence of initial severity of depression on effectiveness of low intensity interventions: meta-analysis of individual patient data

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STUDY QUESTION Do patients with more severe depression benefit less from "low intensity" psychological therapy than those with milder depression?

SUMMARY ANSWER No, patients with more severe depression show at least as much clinical benefit from low intensity interventions as less depressed patients.

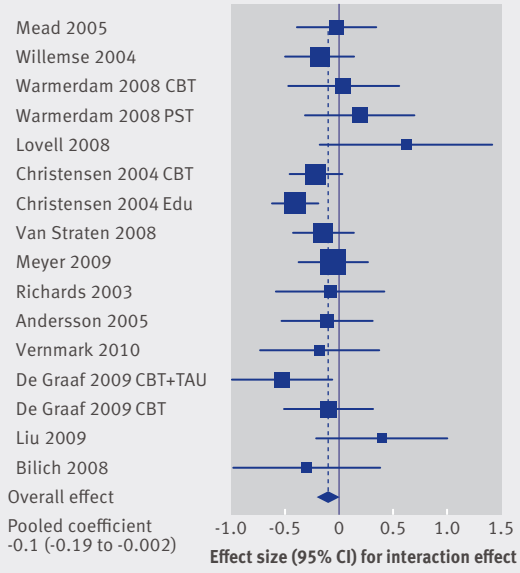
WHAT IS KNOWN AND WHAT THIS PAPER ADDS
To better manage the high prevalence of depression in the community, many services seek to provide simple forms of psychological therapy (low intensity interventions), but whether patients with more severe depression are suitable for such interventions is not known. We found no clinically meaningful differences in treatment effects between more and less severely ill patients receiving low intensity interventions.

SELECTION CRITERIA FOR STUDIES We searched published systematic reviews, updated with a search of the Cochrane Library, for randomised controlled trials of low intensity interventions (such as interventions provided through written materials or the internet with limited professional support) in patients with depression.

Primary outcome(s)
Our primary outcome was the relation between initial depression severity (measured with the Beck Depression Inventory or Center for Epidemiologic Studies Depression Scale) and the amount of clinical benefit (change in depression score) that patients received from low intensity interventions.

Main results and role of chance
We used individual patient data from 16 trials including 2470 patients. We found a significant interaction between baseline severity and treatment effect (coefficient −0.1 (95% CI −0.19 to −0.002)), suggesting that patients who are more severely depressed at baseline demonstrate larger treatment effects from low intensity interventions than those who are less severely depressed. However, the magnitude of the interaction was small and may not be clinically significant.

Interactions between baseline severity of depression and effect of low intensity interventions



CBT=cognitive behavioural therapy; TAU=treatment as usual; PST=problem solving therapy; Edu=education

Bias, confounding, and other reasons for caution
We were unable to access all published data on low intensity interventions, obtaining individual patient data from just over half of the 29 eligible studies. Although we found no clinically meaningful differences in treatment effects between more and less severely ill patients receiving low intensity interventions, patients with more severe depression are more likely to continue to show clinically significant levels of distress after low intensity treatments and may require additional care.

Study funding/potential competing interests
The study was funded as part of the UK National Institute of Health Research (NIHR) School for Primary Care Research. BM is an employee of GAIA AG, Hamburg, which owns one of the low intensity interventions considered in this paper. PB has been a paid consultant to the British Association for Counselling and Psychotherapy.

Comparative effect sizes in randomised trials from less developed and more developed countries: meta-epidemiological assessment

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STUDY QUESTION Do randomised trials in less developed countries give different results from those in more developed countries and, if so, to what extent?

SUMMARY ANSWER Randomised trials from less developed countries occasionally show significantly different treatment effects from those from more developed countries, and on average treatment effects are more favourable in the less developed countries.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

An increasing number of trials are performed in less developed countries with no longstanding tradition of clinical research. Discrepancies in treatment effects between trials from more developed versus less developed countries may often reflect biases as well as genuine differences and should be taken into account when generalising evidence across different settings.

Selection criteria for studies

A meta-epidemiological assessment was performed of trials from less and more developed countries identified through the Cochrane database of systematic reviews. We selected Cochrane meta-analyses with mortality outcomes including quantitative data from at least one randomised trial from a less developed country and at least one trial from a more developed country. For each meta-analysis we compared the relative risk estimates of more developed versus less developed countries by calculating the relative relative risk (RRR) for each topic and the summary relative relative risk (sRRR) across all topics. Additionally, we performed similar analyses for the primary binary outcome of each eligible topic.

Primary outcome

The primary outcome of the current study was the discrepancy in effect estimates on mortality between trials from less developed and more developed countries.

Statistically significant differences in treatment effects on mortality between trials from less developed and more developed countries

Topic	Experimental intervention	Outcome	Relative relative risk (95% CI) for more *v* less developed countries
Antenatal prevention in preterm birth	Corticosteroids	Fetal and neonatal deaths	2.08 (1.30 to 3.33)
Antioxidant supplements for prevention	Antioxidants	Mortality	1.13 (1.01 to 1.27)
Multiple pregnancy	Admission to hospital for bed rest	Perinatal death	4.42 (1.03 to 18.99)
Treatment of sepsis and septic shock	Corticosteroids	All cause mortality at 28 days	2.58 (1.01 to 6.63)
Prevention of gastrointestinal cancers	Antioxidants	Mortality	1.15 (1.03 to 1.29)
Non-neutropenic critically ill patients	Systemic antifungals	Mortality	3.18 (1.08 to 9.40)
Treatment of non-small cell lung cancer	Postoperative radiotherapy	Mortality	1.61 (1.03 to 2.53)
Aneurysmal subarachnoid haemorrhage	Calcium antagonists alone	Case fatality	5.73 (1.13 to 28.3)
Prevention of infection in preterm or low birthweight infants	Intravenous immunoglobulin	All cause mortality	1.93 (1.01 to 3.66)
Unresectable hepatocellular carcinoma	Transarterial (chemo) embolisation	All cause mortality	1.76 (1.05 to 2.97)
Oral cavity and oropharyngeal cancer	Altered fractionation radiotherapy	Total mortality	1.60 (1.03 to 2.48)

Main results and role of chance

139 meta-analyses with mortality outcomes were eligible. No nominally significant differences between the country types were found for 128 (92%) meta-analyses. However, differences were beyond chance in 11 (8%) cases (antenatal corticosteroids, preventive antioxidants, admissions to hospital for bed rest in multiple pregnancy, steroids in sepsis, antioxidants for the prevention of gastrointestinal cancer, antifungals for critically ill patients, postoperative radiotherapy for non-small cell lung cancer, calcium antagonists in aneurysmal subarachnoid haemorrhage, intravenous immunoglobulin for preventing infection in preterm or low birthweight infants, transarterial embolisation in unresectable hepatocellular carcinoma, and altered fractionation radiotherapy for oral cavity and oropharyngeal cancer), always showing more favourable treatment effects in trials from less developed countries. The sRRR was 1.12 (95% confidence interval 1.06 to 1.18; $P<0.001$; $I^2=0\%$), suggesting significantly more favourable mortality effects in trials from less developed countries. Results were similar when focusing on meta-analyses with nominally significant treatment effects for mortality (sRRR 1.15), excluding meta-analyses of old trials (1.14), and excluding trials from less developed countries subsequently becoming more developed (1.12). For the primary meta-analysis binary outcomes (127 eligible meta-analyses), 20 topics had differences in treatment effects in more developed versus less developed countries beyond chance (more favourable in less developed countries in 15/20 cases).

Bias, confounding, and other reasons for caution

Publication bias or selective analysis and outcome reporting biases may be influential in shaping these findings. A higher barrier to publication for authors from less developed countries with no longstanding tradition in clinical research may further boost selective reporting. Large, well conducted trials are needed to probe the claims for country specific major benefits and they may show that many of these claims are spurious. Moreover, differences in treatment effects between less developed and more developed countries may also be due to genuine differences rather than to biases. Low income and middle income countries face substantial financial barriers to their total healthcare budget, which may limit the implementation of expensive interventions. However, we did not identify any discrepancies where the implicated intervention was expensive or difficult to administer and its efficacy may have depended largely on sophisticated background standards of care. Nevertheless, differentiating between bias and genuine differences in baseline risks or treatment implementation might be difficult. These concerns should be taken into account when generalising evidence across different settings.

Features of effective computerised clinical decision support systems: meta-regression of 162 randomised trials

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"Can the authors provide a list of excluded articles? For example, why was the positive study by Kucher et al not included?" Robert G Badgett, physician, Kansas

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Editorial:The road to effective clinical decision support: are we there yet? (*BMJ* 2013;346:f1616)

STUDY QUESTION

What characteristics differentiate computerised clinical decision support systems that successfully improve clinical care or patient outcomes from those that do not?

SUMMARY ANSWER

Presenting advice within electronic charting or order entry systems is not sufficient to derive clinical benefit and is associated with failure, perhaps from alert fatigue. Demanding reasons from clinicians before they can over-ride advice and also providing recommendations to patients might improve chances of success.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Computerised clinical decision support systems often fail to improve the process of care and are even less likely to improve patient outcomes. Our study found that presenting decision support within electronic charting or order entry systems is not sufficient to derive clinical benefit and is associated with failure. Demanding reasons from clinicians before they can over-ride electronic advice and providing advice to patients and clinicians might improve chances of success. Most evaluations have been conducted by the developers of the systems and such evaluations are more likely to show benefit than those conducted externally.

Studies and setting

We created a database of characteristics and effectiveness of computerised support systems in 162 randomised controlled trials from a recent systematic review.

Design

In this cross sectional study, we conducted logistic regression analyses to determine the association between characteristics and effectiveness of computerised clinical decision support systems. We used several statistical methods for sensitivity analysis.

Primary outcomes

We defined effectiveness as a significant difference in favour of the system over control for process of care (such as adherence to prescribing recommendations) or patient outcomes (such as reduction in blood pressure, mortality). In a multivariable model, we looked for associations between system effectiveness and whether the system provided advice that was automatically within clinical workflow, given at the time of care, presented in an electronic charting or order entry system, required reasons to be given for over-riding advice, and was also given to patients, and whether some of the study's authors were also the system's developers.

Main results and the role of chance

Computerised clinical decision support systems presenting advice in electronic charting or order entry interfaces were less likely to succeed than their counterparts (odds ratio 0.37, 95% confidence interval 0.17 to 0.80). Systems more likely to succeed than their counterparts provided advice for patients in addition to practitioners (2.77, 1.07 to 7.17), required practitioners to give a reason when over-riding advice (11.23, 1.98 to 63.72), or were evaluated by their developers (4.35, 1.66 to 11.44).

Bias, confounding, and other reasons for caution

Though our study was based on data from randomised controlled trials, our analyses were observational. We did not find significant associations for the remaining 17 factors tested in exploratory analyses but cannot rule out confounding by factors that we could not test directly, such as leadership and a culture of quality improvement. Our findings were generally robust across different statistical methods and in internal validation, but the estimates of effect were imprecise. Additional studies are needed—ideally randomised controlled trials directly comparing different features.

Generalisability to other populations

Commercial products represent only 21% of systems tested in our trials but will account for nearly all systems clinicians will use. While we found no association between commercial status and success, we did not have sufficient data to test interactions between commercial status and system features and cannot determine if the associations we discovered are generalisable to commercial products. Over a third (37%) of trials were conducted at institutions with an academic history in medical informatics, but we found no link between this and effectiveness.

Odds ratios (95% confidence intervals) and P values for adjusted associations between effectiveness and features of computerised clinical decision support systems

Factors	Prespecified model (148 trials)	Final primary model (150 trials)
Developed by authors	3.52 (1.34 to 9.27), 0.008	4.35 (1.66 to 11.44), 0.002
Advice automatically in workflow	1.48 (0.62 to 3.52), 0.38	—
Advice at time of care	0.61 (0.21 to 1.77), 0.35	—
Advice presented in electronic charting or order entry	0.33 (0.14 to 0.76), 0.008	0.37 (0.17 to 0.80), 0.01
Provides advice for patients	2.54 (0.98 to 6.57), 0.05	2.77 (1.07 to 7.17), 0.03
Requires reason for over-ride	10.69 (1.87 to 61.02), 0.001	11.23 (1.98 to 63.72), <0.001

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Cognitive function and other risk factors for mild traumatic brain injury in young men: nationwide cohort study

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EDITORIAL by Newcombe and Menon

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STUDY QUESTION

Does a mild traumatic brain injury result in lower cognitive function?

SUMMARY ANSWER

Cognitive function was similar in men with mild traumatic brain injuries before and after cognitive testing.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous retrospective studies have found lower cognitive function after a mild traumatic brain injury in several areas including attention, working memory, episodic memory, verbal learning, and processing speed. Low cognitive function was found in men who later sustained mild traumatic brain injuries, suggesting that low cognitive function may be a risk factor rather than the long term consequence of such injuries.

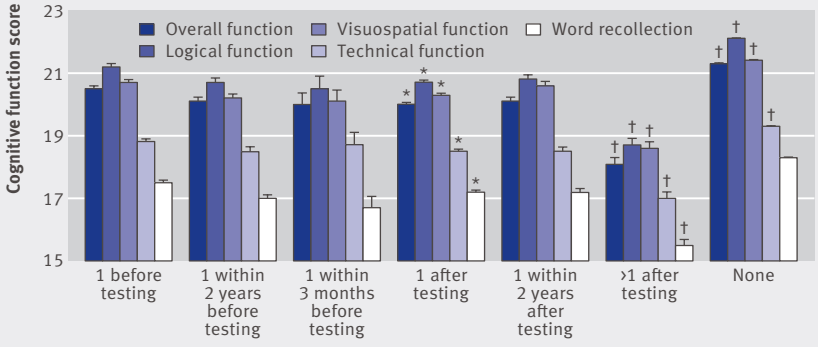
Participants and setting

We studied a nationwide cohort of 305 885 men conscripted for mandatory Swedish military service between 1989 and 1994 at a mean age of 18 years.

Design, size, and duration

We constructed a measure of overall cognitive function from the four different tests used at conscription. We investigated mild traumatic brain injuries occurring before and after conscription in relation to cognitive function and other potential risk factors assessed at conscription and follow-up.

Cognitive function at conscription for total cohort based on mild traumatic brain injury status at follow-up



* Significantly lower (P<0.01) for specific test compared with men with one mild traumatic brain injury before cognitive testing (n=4713)
† Significantly different (P<0.01) for specific cognitive test compared with all other groups

Main results and the role of chance

In the cohort, 4713 men had sustained one mild traumatic brain injury before the tests of cognitive function. In the rest of the cohort, 11 217 men sustained one mild traumatic brain injury, and 795 men sustained at least two such injuries after cognitive testing, during a median follow-up period of 19 (range 0–22) years. Men with one injury within two years before (n=1988) or after cognitive testing (n=2214) had about 5.5% lower overall cognitive function scores than men with no injury during follow-up (P<0.001 for both). Men with at least two injuries after cognitive testing (n=795) had 15% lower overall cognitive function scores than those with none (P<0.001). Men with a mild traumatic brain injury within three months before cognitive testing had similar cognitive function scores to men with an injury within two years after the cognitive tests. Independent strong risk factors ($P<1\times10^{-10}$) for at least one mild traumatic brain injury after cognitive testing (n=12 494 events) included low overall cognitive function, a previous mild traumatic brain injury, hospital admission for intoxications, and low education and socioeconomic status. In a sub-cohort of twin pairs in which one twin had a mild traumatic brain injury before cognitive testing (n=63), both twins had lower logical performance and technical performance compared with men in the total cohort with no injury (P<0.05 for all). These results may suggest a genetic component to the low cognitive function associated with mild traumatic brain injury.

Bias, confounding, and other reasons for caution

We evaluated only younger men with mild traumatic brain injury, so our results are not applicable to women, older men, or people with more severe traumatic brain injuries.

Generalisability to other populations

The large well characterised nationwide cohort studied including more than 16 000 diagnosed mild traumatic brain injuries increases external validity.

Study funding/potential competing interests

The study was funded by the Swedish Research Council.