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IS TREATMENT OF DEPRESSION COST-EFFECTIVE IN PEOPLE WITH DIABETES? A SYSTEMATIC REVIEW OF THE ECONOMIC EVIDENCE

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Objectives: Depression is common in diabetes and linked to a wide range of adverse outcomes. UK policy indicates that depression should be treated using conventional psychological treatments in a stepped care framework. This review aimed to identify current economic evidence of psychological treatments for depression among people with diabetes.
Method: Electronic search strategies (conducted in MEDLINE, EMBASE, PsycINFO, CINAHL, NHS EED) combined clinical and economic search terms to identify full economic evaluations of the relevant interventions. Prespecified screening and inclusion criteria were used. Standardized data extraction and critical appraisal were conducted and the results summarized qualitatively.
Results: Excluding duplicates, 1,516 studies for co-morbid depression and diabetes were screened. Four economic evaluations were identified. The studies found that the interventions improved health status, reduced depression and were cost-effective compared with usual care. The studies were all U.S.-based and evaluated collaborative care programs that included psychological therapies. Critical appraisal indicated limitations with the study designs, analysis and results for all studies.
Conclusions: The review highlighted the paucity of evidence in this area. The four studies indicated the potential of interventions to reduce depression and be cost-effective compared with usual care. Two studies reported costs per QALY gained of USD 267 to USD 4,317, whilst two studies reported the intervention dominated usual care, with net savings of USD 440 to USD 612 and net gains in patient free days or QALYs.

Keywords: Cost-effectiveness, Systematic review, Diabetes, Depression

Major depression, a common disabling clinical condition, affects 21/1000 (point prevalence) 16 to 65-year-olds in the United Kingdom. The lifetime prevalence in individuals with diabetes is 24 percent (1), three times higher than the general population. Clinically relevant depression affects around 30 percent of patients with diabetes and depression (2). People with diabetes plus depression are less likely to be physically and socially active, effectively communicate with healthcare practitioners or comply with diet and treatment than people with diabetes alone. These factors can lead to worse long term complications and higher mortality (3;4). Problems with detection and treatment of depression are compounded by long term conditions and patients and healthcare professionals normalize symptoms of depression and distress (5).

The NIHR funded Collaboration for Leadership in Applied Health Research and Care (CLAHRC) in Greater Manchester, focuses on chronic vascular conditions. Within this program, the Practitioner Theme is concerned with improving access and quality of care for people with co-morbid depression and diabetes/CHD. The work reported in this paper was funded as part of this program of work. Three of the authors (Jeeva, Bundy, and Davies) are also part of the Manchester Academic Health Sciences Centre. Dickens is part of the University of Exeter and Peninsula Collaboration for Leadership in Applied Health Research and Care (PenCLAHRC).

In the UK, depression is ordinarily managed in primary care. UK government policy promotes increased access to mental health care through commissioning and provision of health and social care in primary care settings, supported by the Improving Access to Psychological Therapies (IAPT) initiative and cross governmental strategy to improve the balance between mental and physical health care. Policy initiatives to improve access to and quality of low-intensity interventions such as talking therapies focused on innovations in service delivery in primary care.

Management in primary care can support patients and practitioners in avoiding talking about depression (5;6). This is reinforced by highly managed and time-limited GP consultations in UK primary care (7). Mental health services are separated from general practice, with poor access to psychological services, hindering integrated, effective treatment (8).

Effective care for depression in patients with diabetes requires changes in the attitudes, beliefs and behaviors of healthcare practitioners, with care models based on educational and organizational changes in primary care (9). Collaborative care models that include psychological interventions may be effective and cost effective in people with depression or long term

conditions when healthcare systems are barriers to effective treatments (10–12). Qualitative research and a systematic review of psychological interventions to manage depression in diabetes indicated the need for new approaches to overcome the barriers to using evidence based interventions in long term conditions (5;13).

However, decision makers need information about the relative costs, benefits and cost-effectiveness to inform policy and practice changes to implement new interventions. This study reports a focused systematic review of the cost-effectiveness of psychological interventions in people with depression and diabetes. The aims were to: (i) Identify and review current economic evidence of interventions for people with diabetes and co-morbid clinically relevant depression. (ii) Identify the level of robustness or uncertainty of economic evidence about the management of co-morbid depression (with diabetes). (iii) Inform the design of prospective studies to support evidence based policy and practice and identify key data to collect.

METHODS

Search Strategy

The search strategy (Supplementary Table 1, which can be viewed online at http://dx.doi.org/10.1017/S0266462313000445, shows the final search used in Medline) combined economic search terms (14), with clinical terms from a previous review (13) and validated by checking whether it identified publications known to the research team. Electronic searches were limited to January 2000 to May 2012. Older studies may not reflect current service organization, provision or funding which have changed substantially in recent years. The search strategy was adapted for each of the electronic databases searched, using the Ovid interface: Medline, Embase, PsycINFO, CINAHL, and NHS Economic Evaluation Database (NHS EED) databases.

Inclusion Criteria

Studies were included if they were published in English, reported full economic evaluations with a synthesis of net costs and outcomes in adults, compared two or more interventions to manage depression in people with diabetes. Policy papers, cost of treatment or burden of illness studies, letters, editorials, book reviews and poster presentations were excluded.

Data extraction and Assessment

Two authors (FJ and LD) screened titles and abstracts and differences were resolved by discussion. Full papers were obtained for titles and abstracts that met the inclusion criteria or were uncertain. Full papers were assessed for inclusion in the review. Data were extracted and critically assessed on a standardized form by FJ and LD, using NHS EED guidelines (14) and descriptively summarized using narrative tables.

RESULTS

Figure 1 summarizes the number of studies retrieved and reasons for exclusion. Four economic evaluations alongside or integrated with randomized controlled trials (RCT) were included (15–18) and are summarized in Table 1 (and Supplementary Table 2, which can be viewed online at http://dx.doi.org/10.1017/S0266462313000445). None of the four studies reported all the detail about participants and methods required for the summary tables or critical appraisal. Previously published reports of the evaluations were used to identify this information.

Target Population and Participants

All studies were conducted in the United States and the target population was people with major depression and diabetes (15–17) and/or coronary heart disease (CHD) (18). In one study (15) the target population was elderly people (60 years or more) with major depression. For this study, a sub-group of participants included in the original study (19) who also had diabetes were analyzed.

In one study, the majority of participants were predominantly Hispanic people. The authors noted this group were at higher risk of diabetes and co-morbid diabetes and depression than non Hispanic white people (17). In one study 23 percent to 30 percent of participants had coronary heart disease (CHD) (18), whilst 82 percent to 89 percent had diabetes with or without CHD. This study did not present results separately for diabetes and CHD. There appeared to be differences in demographic characteristics between the usual care and intervention groups in all but one of the studies (16–18).

Interventions

All studies evaluated collaborative care to help participants manage depression in primary care. They included a care planning process of stepped depression management tailored to individual needs, care manager, psychological therapy and/or antidepressant therapy. One study (18) actively targeted diabetes (or CHD) in the care plans. Care managers delivered psychological therapy and were trained/specialist nurses, incorporated into the primary care team. They were supervised by psychiatrists and/or primary care physicians to monitor progress and adjust treatment plans according to treatment response. Care managers contacted participants two to three times per month initially to monitor and discuss progress.

Usual care was not described in any of the papers.

Costs and Outcomes

One study reported a cost-effectiveness analysis (16) whilst cost-utility analyses were presented in the other three evaluations (15;17;18). All but one of the studies (17) used a time horizon of 24 months (15;16;18), but costs and outcomes were not discounted in any of the analyses. Three studies reported a payor perspective (16–18) and one reported a societal viewpoint for the analyses (15;19). Tables 2 and 3

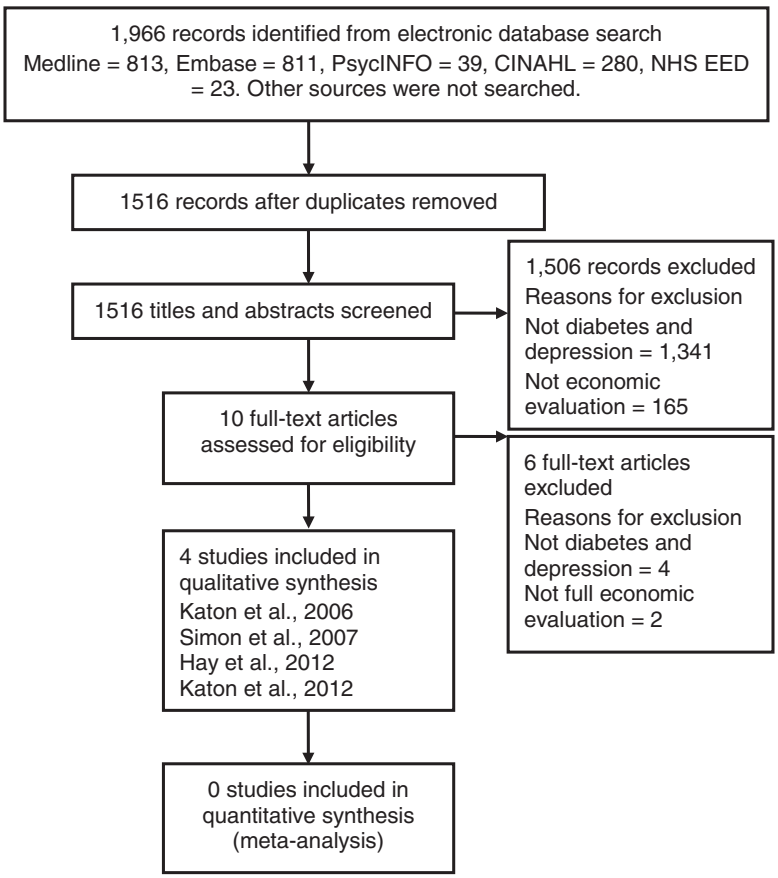

Figure 1. Studies identified and retrieved published between 2000 and May 2012.

summarize the costs and outcomes. Costs are adjusted to a single price year (USD 2011), using a medical care services index (20). Total costs of the intervention group were USD22,250 to USD29,100 over 24 months, whilst total costs of the comparator were USD21,900 to USD31,200 (15; 16; 18). One study (17) did not report the total costs of care. The authors found no statistically significant differences in the change in costs from 6 months prebaseline to the 18 month follow-up. On this basis they assumed that the only cost attributable to the intervention was the cost of providing the intervention so only included the additional costs of the intervention with the costs of the comparator assigned as zero (17).

Three studies reported net savings (USD440-USD1206) for the intervention (15;16;18). The 95 percent confidence intervals (CIs) all cross zero, suggesting no statistically significant difference in costs between intervention and control groups. One study reported a net cost (USD 548; 17).

Different measures were used to assess the impact of care. Outcomes were reported for the intervention and control group in two studies. These were depression free days (412 depression free days, intervention *vs*. 359 depression free days control; 16) and QALYs (1.05 intervention *vs*. 0.92 control; 17). Three studies reported net QALYs (0.063 to 0.335 QALYs gained), and two studies reported monetary measures of net benefit (USD 1212 to USD 1520).

Table 3 reports the net costs, outcomes and incremental cost-effectiveness ratio (ICER) of the interventions evaluated. These indicate less variation in the data.

Critical Assessment

Risk of bias. Double blinding treatment providers and patients was not feasible and all studies used blinded assessments, data entry and analysis. Whether this was successful was not reported.

Individual participants were randomized, increasing risk of contaminating practice and treatment between allocation groups. Sample size estimates were reported for effectiveness, not economic measures, and excluded cluster effects. Combined with substantial variance in the economic measures, it is unclear if sample sizes were sufficient to accurately estimate the ICER and uncertainty.

One study did not adjust for imbalances in participant baseline characteristics (15). Three studies did adjust for baseline characteristics (16–18), but did not report a-priori identification of characteristics that influence health status or costs. One study included participants with CHD and no diabetes, but did not report results separately (18). It is not reported whether there were differences in the interventions' cost-effectiveness or whether people with depression and diabetes are comparable to those with depression and CHD.

Table 1. Study Designs for Evaluations of Interventions for Diabetes and Depression

Study (year)	Katon et al. (2006)	Simon et al. (2007)	Hay et al. (2012)	Katon et al. (2012)
Study participants	Average age: 70 years Gender: 52%–54% female Ethnicity: 64%–65% white	Average age: 57–58 years Gender: 34%–35% female Ethnicity: 71%–80% white	Age: 69%–75%> = 50 years Gender: 80%–85% female Ethnicity: 95%–97% white	Average age: 56–57 years Gender: 48%–56% female Ethnicity: 75%–78% white
Intervention and comparator	Intervention: Stepped collaborative care program, including behavioral activation plus problem solving treatment or enhanced anti-depressant medication; $n = 204$	Intervention: Specialist nurse delivered stepped care plan for depression including problem solving psychotherapy or structured anti-depressant pharmacotherapy; $n = 165$	Intervention: structured stepped care intervention including problem-solving therapy and/or antidepressant medication, monthly follow up, and care and service systems navigation assistance; $n = 193$	Intervention: Collaborative care management including nurse care managers to develop individual care plans and provide behavioral interventions plus usual care; $n = 106$
	Comparator: Usual care (details not provided); $n = 214$	Comparator: Usual care (details not provided); $n = 164$	Comparator: Usual care plus educational pamphlets and a community resource list; $n = 194$	Comparator: Usual care plus notification of participants depression status (full details not provided); $n = 108$
Source of effectiveness data	Multi-center RCT in 18 primary care clinics in five states in USA	Multi-center RCT in 9 primary care clinics	RCT in 2 community clinics in Los Angeles County (1 primary care, 1 diabetes care)	Multi-center RCT in 14 primary care clinics in Washington State
Source of resource use and cost data	Detailed records of all patients contacts	Resource use and cost derived from administrative cost records.	Resource use and cost derived from administrative cost records for all patients enrolled in trial	Resource use and cost derived from administrative cost records for all patients enrolled in trial
	Resource use and costs not reported separately	Resource use and costs not reported separately	Resource use and costs not reported separately.	Resource use and costs not reported separately
	Unit cost data not reported	Unit cost data not reported	Some unit costs reported. Medicare and Federal Supply Schedule	Some unit costs reported, from administrative data
Time horizon	24 months	24 months	18 months	24 months

Table 2. Total Costs (USD, 2011) and Patient Benefit

Mean cost		Mean patient benefit	
Intervention	Control	Intervention	Control
Katon et al. (2006) 24 months time horizon			
Mean: 25,250 95% CI: 22,328–28,174	Mean: 26,506 95% CI: 22,205–30,807	Benefit in the intervention group was not reported. Incremental patient benefit reported in Table 3	Benefit in the control group was not reported. Incremental patient benefit reported in Table 3
Simon et al. (2007) 24 months time horizon			
Mean: 29,069 SD: 38,569	Mean: 31,163 SD: 49,853	Depression free days Mean: 412 SD: 202	Depression free days Mean: 359 SD: 207
Hay et al (2012) 18 months time horizon			
Mean cost: 548 95% CI: 499–597	Mean cost: 0.00 95% CI: N.A.	QALYs Mean: 1.05	QALYs Mean: 0.92
Katon et al. (2012) 24 months time horizon (total outpatient costs only)			
Mean: 22,255 95% CI: 18,255–26,258	Mean: 20,897 95% CI: 16,869–24,925	Benefit in the intervention group was not reported. Incremental patient benefit reported in Table 3	Benefit in the control group was not reported. Incremental patient benefit reported in Table 3

Table 3. Net Costs (USD, 2011), Outcomes, and Incremental Cost-Effectiveness Ratios

Authors	Net cost of intervention, USD, 2011	Net benefit of intervention	ICER	Net benefit	Probability of intervention being cost effective
Katon et al 2006	Net cost: −1,206 95% CI: -6,124–3,709	Net depression free days: 115.4 95% CI: 71.7–159.1 Net QALYS: Lower estimate = 0.063 (95% CI 0.039–0.087) Higher estimate = 0.126 (95% CI: 0.079–0.174)	Net cost/depression free day: not reported Net cost/QALY (outpatient costs only): Lower estimate = $267 (95% CI:194–425) Higher estimate = $534 (95% CI: 386–863)	Net benefit: $1,520 95% CI: 932–2,116 at willingness to pay for depression free day of $10	$p = .67$ that intervention is cost saving and effective
Simon et al. 2007	Net outpatient cost: −440 95% CI: −1,410–510	Net depression free days: 61 95% CI: 11–82	Not applicable, intervention dominates	Net benefit: $440 if willingness to pay for a depression free day = $0 Net benefit: $1212 if willingness to pay for a depression free day = $10	Not reported
Hay et al 2012	Net cost: $548	Net QALYs: 0.13	Net cost/QALY: $4,317	Not reported	$p = .50$ if decision makers willing to pay $5,000 to gain 1 QALY $p = .50$ if decision makers willing to pay $12000 to gain 1 QALY
Katon et al 2012	Net outpatient cost: Primary analysis: $−612 95% CI: −3,523–2,115 Sensitivity analysis: $ −1,149 95% CI: −3,881–1,582	Net depression free days: 114 95% CI: 79–149 Net QALYs: 0.335 95% CI: −0.18–0.85	Net cost/depression free day, primary analysis: -$5.42 95% CI: −30.65–20 Net cost/depression free day, sensitivity analysis: -$10.18 95% CI: −36.97–14.6 Net cost/QALY, primary analysis: −$1,826 95% CI: −2,964–2,964 Net cost/QALY, sensitivity analysis: −$ 3,396 95% CI: −4,134–2,804	Not reported	$p = .97$ if decision makers willing to pay $20,000 to gain 1 QALY $p = .50$ if decision makers willing to pay $12,000 to gain 1 QALY

Only two studies accounted for missing data (15;17). Insufficient information was reported to assess the assumptions used and the robustness of the results.

Choice of Comparator. The comparator in all studies was usual care, but what this comprised was not described. The relevance of alternative comparators was not discussed. Differences in usual care between studies may explain some of the variation in the costs and outcomes reported.

Validity of Benefit and Cost Estimates. Three studies reported depression-free days and net monetary values of depression-free days (primary analysis), which exclude adverse events or broader health benefits of the intervention (15;16;18). Different willingness-to-pay values to gain a depression-free day, were used, so are not directly comparable.

One study used the SF-12 and SF-6D tariffs to estimate QALYs (17). The SF-12 does not include all items for the SF-6D, reducing the reliability and validity of the estimated results. Two studies estimated QALYs by mapping published data onto net depression-free days (15), or imputing from diabetes markers (18). This excludes adverse events, reduces the robustness of the QALY estimate and reduces comparability with other evaluations.

Direct nonmedical costs were not reported. Insufficient detail was given to assess the impact of this on cost-effectiveness estimates. Usual care was not described, so it is not clear whether

the range of costs included is appropriate. Total costs in one study only included outpatient costs (18). One study only reported the net additional costs of the intervention (17) excluding costs of other services to manage depression or diabetes. There is insufficient information about the method of identifying and attributing service use to assess the validity of this approach.

Length of follow-up ranged from 18–24 months. No study extrapolated results over patient lifetimes, which is important for diabetes and depression. All studies reported cost-effectiveness acceptability analyses and/or net benefit analyses but did not adequately report the methods or the relevance of the range of willingness to pay thresholds used.

Transferability of Results. None of the studies used sensitivity analysis to explore the transferability of the results to other settings or countries. All studies were conducted in the United States, and one person (Katon) was an author on all four. This may indicate all studies were based in similar healthcare systems and evaluated very similar interventions. If so, generalizability of the intervention and results to other settings/countries, where health care differs may be limited.

All studies were primary care based, using systematic screening to identify eligible patients, which may not be feasible elsewhere. It may also change the service setting, affecting the cost-effectiveness of the intervention. Information about adherence with treatment protocols and therapeutic alliances between healthcare professional and patients was not reported and can influence the transferability of results between settings/countries.

Whether the study samples were representative of the study populations or other populations was unclear. Most participants in one study (16) had Type 2 diabetes (96 percent). Whether participants had Type 1 or Type 2 diabetes was not reported in three studies. The proportion of patients who screened positive for depression and were randomized ranged from 19 percent to 74 percent. The reasons for this variation were unclear.

No study reported unit costs, costs and resource use for all cost items, limiting transferability between settings/countries.

DISCUSSION

Implications for Policy and Practice

This study reports a systematic review of full economic evaluations of interventions to manage depression in people with diabetes. Four studies met inclusion criteria, indicating collaborative care including psychological therapy may be cost-effective.

There were limitations with this review and the studies assessed. This review was focused rather than comprehensive. No hand searches or searches of the grey literature were conducted, meaning key studies may have been missed. All the studies included in the review evaluated models of collaborative care. Collaborative care was not an objective of the review and not explicitly included as a search term in the search strategy. However, the search strategy did include terms relating to psychological or behavioral interventions, which were key elements of the collaborative care approaches. Clinical experts in the research team did not identify any additional evaluations that were not identified in the electronic searches. The search strategy did not explicitly include CHD as a search term, whereas 1 study included participants with depression and diabetes and/or CHD. It is not possible to assess from this study whether the results for the two groups are comparable.

Assessment of the internal validity and robustness of the four studies was limited by the information reported about the study design and methods. All the studies appeared to have limitations in study design that increased the risk of selection and measurement bias. Issues in the measurement of costs and health benefit limit the validity of the estimates.

The generalizability of the results to other settings and countries may be limited. Key issues to consider are first, whether the health systems and organization of care in the studies, (e.g., funding and patterns of service use) are typical of those found in other parts of the United States or other countries. Second, whether the intervention requires highly trained/specialist staff to deliver it to achieve the same level of adherence, therapeutic alliance and effectiveness, and the feasibility and acceptability of this in other settings/countries. Third, whether the predominantly older participant samples are representative of the populations treated in other settings in terms of age, type of diabetes (1 or 2) and main setting of care. A related point is whether screening will be needed to identify patients and whether this is feasible.

Implications for Research

The sample sizes reported may not be sufficient to accurately represent the incremental cost-effectiveness of the intervention or identify important differences in costs or health benefit. Evidence from clinical research demonstrates that small studies are associated with over-estimates of effects. Larger, well controlled, prospective evaluations are needed to inform evidence based policy and practice about cost-effectiveness. The evaluations also need to take into account clustering effects where experience from providing the intervention may influence the type and quantity of care in the comparison group. The studies reviewed provide information to estimate the sample sizes for economic endpoints such as the net benefit statistic.

Work is needed to identify the relevant range of service use. For example, costs of participant and family time (as inputs to the production of care), purchase of care from private providers and the costs of community and social care services are relevant in some settings.

The measure of patient benefit in future evaluations should reflect the impact of care on participants overall health. This is particularly important if psychological therapies indirectly affect adherence and the effectiveness of diabetes care.

Qualitative and quantitative studies are needed to identify, from the patient's perspective, key attributes of health and estimate the relative utility or value of these. The extent to which QALYs and measures to estimate QALYs are relevant to these patient groups should be explored (21).

Evaluations in broader samples of participants are needed. The majority of participants in the studies were older, white women. Screening and selection of participants means they are not representative of all people with diabetes and depression. Future evaluations require procedures to minimize the risk of recruitment bias. Additionally, collecting demographic characteristics of patients who do not participate could facilitate analytic controls for this problem. For example, survey analysis methods to weight participants' data according to over and under-represented characteristics may help to reduce the impact of recruitment biases in the study sample.

Future evaluations should minimize missing observations and data in participants who complete scheduled follow-up as well as encourage complete follow-up. Where missing observations and censored data occur analytic approaches to impute the missing data are required. These should be selected to minimize biases and adequately represent uncertainty.

Economic models are needed to extrapolate the results to other settings and populations, and longer time horizons as well as provide the decision maker with the information required for evidence based policy and practice. This requires more detailed reporting of the methods, assumptions and results of prospective evaluations to support formal synthesis of economic evidence and development and analysis of economic models.

CONCLUSION

A recent Cochrane review concluded that collaborative care is an effective approach to the management of depression and anxiety (22) and there is evidence to support its use in managing co-morbid depression and diabetes (23). Economic evidence suggests that from a U.S. payers perspective, collaborative care to manage depression in people with diabetes is associated with gains in health benefit and may be cost saving. However, as discussed above, there are several issues that limit the relevance of the results to alternative settings, timeframes, and populations. These include differences in health systems and organization of care between settings/countries, the feasibility and acceptability of the intervention in other settings/countries, the selected samples of participants may not be representative of routine practice. Additionally, there is substantial uncertainty about the robustness of the evidence. Variation in results in the studies could reflect differences in: the perspective and range of costs included; the availability and organization of care for long-term conditions and depression between settings and populations; the methods used to estimate costs and benefits; and the characteristics of the study samples recruited.

SUPPLEMENTARY MATERIAL

Supplementary Tables 1 and 2 can be found at: http://dx.doi.org/10.1017/S0266462313000445

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CONFLICTS OF INTEREST

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