

## Article

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[http://dx.doi.org/10.1016/S2215-0366\(14\)00049-2](http://dx.doi.org/10.1016/S2215-0366(14)00049-2)

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# An online programme to reduce depression in patients with multiple sclerosis: a randomised controlled trial

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**Summary Background** With a lifetime risk for major depressive disorder of up to 50%, depression is a common comorbidity in multiple sclerosis but remains widely underdiagnosed and untreated. We investigated the potential of a fully automated, internet-based, cognitive behavioural therapy programme, Deprexis, to reduce depressive symptoms in patients with multiple sclerosis.

**Methods** For this randomised controlled trial, we recruited patients from an outpatient clinic in Hamburg, Germany. Patients aged 18–65 years were eligible for inclusion if they had multiple sclerosis and self-reported depressive symptoms. By use of a computer-generated randomisation sequence, we allocated 90 patients (1:1; no blocking or stratification) to either the intervention group or a waitlist control group for 9 weeks. The primary endpoint was the Beck Depression Inventory (BDI), as assessed by an intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, number NCT01663649.

**Findings** 71 patients completed the trial: 35 patients in the intervention group and 36 patients in the control group. During the intervention, BDI scores decreased in the Deprexis group and increased in the control group, yielding a positive effect of Deprexis relative to the waitlist group (mean group difference  $-4.02$  points [95% CI  $-7.26$  to  $-0.79$ ],  $p=0.015$ , effect size  $d=0.53$ ). Worsening of depressive symptoms from below to above the clinical cutoff (BDI  $>13$ ) occurred in three (7%) of 45 patients in the control group and no patients in the Deprexis group. We noted no adverse events with respect to new occurrence of suicidal ideation during the trial.

**Interpretation** Psychological online-intervention programmes could be suitable for patients with multiple sclerosis who are unable to regularly attend therapeutic sessions because of mobility impairments.

**Funding** European Union and the Deutsche Forschungsgemeinschaft.

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Multiple sclerosis is an inflammatory, demyelinating neurodegenerative disease of the CNS. In addition to motor dysfunction, visual and other sensory impairment, patients with the disorder often have neuropsychiatric symptoms such as depressed mood, fatigue, and cognitive impairment. Depression is especially common in this group of patients who have a lifetime risk for major depressive disorder as high as 25–50%,<sup>1</sup> and a 12 months' prevalence of up to 25%.<sup>2</sup> Depression in multiple sclerosis has been linked to biological as well as psychological factors and substantially affects psychosocial function.<sup>3</sup> Depressive symptoms correlate with decreased quality of life, absence from work, and lower social support in patients with multiple sclerosis.<sup>4,5</sup> Depression is also associated with lower immunotherapy adherence rates and might thus have direct consequences for overall health outcome.<sup>6</sup> Moreover, depression is one of the main predictors for suicidal ideation and suicide risk in patients with multiple sclerosis.<sup>7</sup> If left untreated, depressive symptoms in multiple sclerosis rarely remit spontaneously, often become chronic,<sup>8</sup> and can worsen over time, particularly in patients with scores indicative of clinical depression at the study baseline.<sup>9</sup> Despite its immediate clinical relevance, depression remains widely underdiagnosed and untreated in patients with multiple sclerosis.<sup>10</sup>

We are aware of only two previous placebo-controlled, randomised trials to have assessed the effects of pharmacotherapy with desipramine and paroxetine in depression in patients with multiple sclerosis.<sup>11,12</sup> Findings from a Cochrane review<sup>13</sup> showed that some benefits were apparent—albeit not statistically significant for most endpoints—but that adverse side-effects such as nausea and headaches were a concern. Findings from a systematic review and meta-analysis suggested that cognitive behavioural therapy (CBT) might be beneficial in reducing depressive symptoms in patients with multiple sclerosis.<sup>14</sup> However, the American Academy of Neurology's 2014 guidelines for psychiatric disorders in patients with multiple sclerosis have pointed out that more research is needed.<sup>15</sup> In particular, a need exists to develop and rigidly test the efficacy of treatment strategies for multiple-sclerosis-associated depression and to facilitate access to these treatments. Because multiple sclerosis often causes motor impairment and decreased mobility as well as increased fatigue and cognitive problems, remote access options for psychotherapy might be useful to enhance availability of effective depression interventions such as CBT for these patients. For example, psychotherapy delivered by phone has been shown to decrease depressive symptoms in patients with multiple sclerosis.<sup>16,17</sup> Such approaches, however, still require

availability of a trained psychotherapist.

We tested the feasibility and efficacy of a fully automated, internet-based CBT (iCBT) programme (Deprexis),<sup>18</sup> which has been shown to be effective in patients with depression without comorbid somatic disorders,<sup>19</sup> to reduce depressive symptoms in patients with multiple sclerosis.

## Methods

### Study design and population

In this randomised controlled trial, we contacted by mail patients registered in the database of the multiple sclerosis outpatient clinic at the University Medical Centre Hamburg-Eppendorf, Germany, whose scores from their last clinical visit indicated depressive symptoms (as measured by the mood subscale of the Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS)).<sup>20</sup> Additionally, we recruited participants via online forums following guidelines of the Hamburg Department of Data Security. Participation was free of charge.

Patients were eligible for inclusion if they were aged 18–65 years, had a diagnosis of multiple sclerosis, self-reported depressive symptoms, and willingness to self-administrate iCBT sessions for 9 weeks. Participants were excluded if they did not consent to participation, were diagnosed with bipolar or schizophrenia spectrum disorders, had substantial neurocognitive impairment such as dementia, or had suicidal ideations. We used a secure online-survey programme (EFS survey) to screen for inclusion and exclusion criteria before randomisation. A subgroup of the total sample volunteered to complete in-person visits to our multiple sclerosis outpatient centre before and after the intervention. The aim of this subgroup analysis was to validate depressive symptomatology by means of additional questionnaires and structured interviews.

Written informed consent was provided via the online platform. The study was approved by the ethics committee of the German Society of Psychology.

### Randomisation and masking

We allocated eligible patients to either intervention group or a waitlist control group (WLC; 1:1) using a computer-generated randomisation sequence with no stratification or blocking. JS was in charge of generating the random sequence. None of the other investigators had access to the random sequence at any time. Patients were allocated strictly according to the order (date and exact time of day) in which they had completed the online check of eligibility and baseline assessments of questionnaires as logged by the unipark system, ensuring that the eligibility check was blind to treatment allocation (concealed allocation). JS later was responsible for sending standardised email reminders to complete the online survey to every participant at pre-defined times for follow-up assessment and contributed to writing the report.

Masking of the participants regarding treatment allocation was not possible due to the nature of the information (ie, behavioural intervention). All outcome measures were collected via an automated online interface, so that masking of the assessors was not necessary. For the subgroup in which outcome measures were collected in person, we made substantial effort to ensure that all patients were assessed by a clinician masked to group assignment—ie, the appointments were scheduled and patients were debriefed by staff members not involved in their assessment, and participants were instructed not to reveal their group assignment to the examiners at the clinic.

## Procedures

Deprexis is an online programme based on principles of CBT. It consists of ten sequential modules—psycho-education, behavioural activation, cognitive modification, mindfulness and acceptance, interpersonal skills, relaxation, physical exercise and lifestyle modification, problem solving, expressive writing and forgiveness, positive psychology, and emotion-focus interventions—plus an introduction and a summary module. It implements the technique of simulated dialogue by giving the user multiple-choice options and tailors the subsequent options to the patient's responses. The user's responses thus determine the course of each module. Dependent on the user's speed, each module can be completed in less than 60 mins. The programme is described in detail elsewhere.<sup>18</sup> Participants randomly assigned to the control group were offered full access to Deprexis on completion of the study.

## Outcomes

All outcome measures—a set of questionnaires administered online to measure depressive symptoms, quality of life, and fatigue—were obtained at baseline

### *Figure 1: Trial chart*

and 9 weeks after enrolment (ie, before and after the 9 week long programme for the Deprexis group and before and after waiting for 9 weeks for the waitlist group). We did a follow-up assessment 6 months after the end of the intervention using the same online platform.

Self-report questionnaires obtained online are similar to written questionnaires in terms of reliability and validity,<sup>21</sup> as shown for depression scales including the Beck Depression Inventory (BDI).<sup>22</sup>

The primary endpoint of the study was severity of depressive symptoms as measured by the BDI.<sup>23</sup> We analysed the BDI total score (primary endpoint) as well as BDI subscale scores (post-hoc analysis). The secondary endpoints were quality of life, as measured by the WHO Quality of Life scale (WHO-QoL BREF),<sup>24</sup> disease-related quality of life (measured by HAQUAMS),<sup>20</sup> and fatigue (Fatigue Scale For Motor And Cognitive Function; FSMC).<sup>25</sup> We also screened for suicidal ideation and behaviour (with Suicide Behaviors Questionnaire- Revised [SBQ-R]), as a predefined safety measure.<sup>26</sup>

In the clinical subgroup, patients underwent a structured clinical interview (The Mini International Neuropsychiatric Interview; MINI)<sup>27</sup> administered by a trained clinician. They also

completed an additional depression questionnaire (Inventory of Depressive Symptomatology; IDS-30SR).<sup>28</sup> In this subgroup, we analysed the IDS total score as well as published IDS cognitive and somatic subscales.<sup>29</sup>

To assess treatment adherence we used data from the Deprexis interface, which tracks usage time of each participant. The usage log of Deprexis uses 5-min blocks and excludes each block of inactivity so that the logged usage times is a good estimate of time spent working with the programme. To assess the acceptance of Deprexis by patients, we obtained retrospective appraisal of the programme from participants randomised to the Deprexis group (appendix A).

We did not include a data monitoring committee to assess adverse events. However, we collected self-reported data for suicidal ideation and behaviour using the SBQ-R as a pre defined safety measure. If responses indicated acute risk of suicide (response 3a or 3b on SBQ-R item 3 plus score of 5 or 6 on SBQ-R item 4), patients were provided automatically with emergency contact numbers on the computer screen. To test for incidental evidence of adverse events, we also used a lower threshold for suicidal ideation (score >1 on item 9 of the BDI or score >3 on item 4 of the SBQ-R). We also regarded worsening of depressive symptoms during the trial from below to above the cut-off for so-called caseness for clinical depression (BDI >13) as an adverse event.

## Statistical analysis

Power calculation for the trial was based on results obtained from a previously published study using Deprexis in a cohort of patients with psychiatric disorders without comorbid somatic disorders.<sup>18</sup> The pre-post

See [Online](#) for appendix A

-insert table here-

Data are n (%) or mean (SD). HAQUAMS=Hamburg Quality of Life Questionnaire in Multiple Sclerosis. NaSSA=noradrenergic and specific serotonergic antidepressant. SNRI=selective serotonin and noradrenaline reuptake inhibitors. SSRI=selective serotonin reuptake inhibitor. TCA=tricyclic antidepressants.

### **Table 1: Baseline characteristics**

The effect size observed in that study was  $d=0.58$  and the between-group effect size was  $d=0.64$ . A power calculation with 80% power and  $\alpha$  set at 0.05 with  $d=0.64$  would result in a total sample size of 80 participants. We See [Online](#) for appendix B and C

using ANCOVA models. Here, change from baseline (calculated by subtracting pre-treatment scores from post-treatment scores) of the outcome measure was entered as the dependent variable and baseline scores as the covariate. As recommended by EMA, this model did not include treatment by covariate interactions. We treated missing data as last observation carried forward (LOCF) in the primary intention-to-treat analysis. We provide mixed models and multiple imputations (20 imputations using sex, age, group, and baseline BDI as predictors) as sensitivity analyses. We also include an analysis of patients with complete data before and after the treatment period (as per protocol). Raw data of the primary outcome BDI as well as imputed datasets are available in appendix B and appendix C, respectively.

We analysed dichotomous endpoints indicating caseness (BDI below *vs* above the cut-off; diagnosis of major depressive disorder based on the MINI structured interview) using Cochran's  $\chi^2$  test. All analyses of caseness were restricted to patients in whom caseness was established before and after intervention (as per-protocol sample). We used the categorical analyses to provide estimates for number needed to treat. Type I error was set at 5% and all tests were two-tailed. We provide effect sizes as Cohen's *d* ([change Deprexis minus change WLC] divided by SD of the change score). We used PASW statistics software (version 18.0) for all analyses.

This trial is registered with ClinicalTrials.gov, number NCT01663649.

**Figure 2: Effects of Deprexis on Beck Depression Inventory (BDI) scores** Datapoints are mean score and error bars are SD.

conservatively estimated the sample size at 100 patients because the effect size in psychiatric disorders might not readily be translated to patients with neurological disorders and comorbid depression.

Visual inspection of Q-Q plots suggested normal distribution of data. Therefore, we did statistical analyses using parametric tests. According to guidelines for statistical analysis of clinical trials published by the European Medicines Agency (EMA; codes CPMP/ICH/363/96 and CPMP/EWP/2863/99), we did an intention-to-treat analysis for the primary outcome (BDI)

-insert table here-

Data are mean (SD) unless otherwise stated. BDI=Beck Depression Inventory. FSMC=Fatigue scale for Motor and Cognitive function. HAQUAMS=Hamburg Quality of Life Questionnaire for Multiple Sclerosis. WHO QoL BREF=WHO Quality of Life scale.

**Table 2: Treatment effects**

## Role of funding source

The funding sources did not play any role in data collection, analysis, and interpretation of the data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

## Results

Patients were enrolled from July 16, 2012, to Oct 22, 2013. We screened 241 patients and randomised 90 to either the Deprexis or the control group (figure 1). The number of patients who did not complete the 9-week trial period was similar between the two groups (Deprexis *n*=10 [22%]; control *n*=9 [20%]). Baseline characteristics were much the same between the two groups (table 1).

Analysis of the primary endpoint BDI showed a statistically significant treatment effect of Deprexis (figure 2 and table 2). Group differences were slightly larger in the mixed models, multiple imputations, and the per-protocol analyses (appendix A).

BDI subscale analyses showed significant treatment effects on the subdomains of negative attitude towards self and somatic symptoms (table 2).

We also analysed the BDI as a categorical variable (BDI 0–13 vs BDI >13) in the per-protocol sample post-hoc analysis). Between baseline and week 9, the number of patients above the cutoff for clinical depression decreased in the Deprexis group and increased in the control group (p for between-group treatment difference=0.01; figure 3). Based on the BDI categorical analysis, the number needed to treat was eight.

34 participants (Deprexis n=17; control n=17) from the online cohort volunteered to undergo additional psycho-diagnostic assessment. In this subsample, we confirmed a positive treatment effect of Deprexis on the BDI (LOCF p=0.047; d=0.75; appendix A). Similarly, depressive symptoms along DSM-IV diagnostic criteria as measured by the IDS showed a significant treatment effect (LOCF p=0.02; d=0.95; appendix A). Furthermore, we detected treatment effects in the IDS cognitive subscale (LOCF p=0.02, d=0.88) but not in the somatic subscale (appendix A). The proportion of patients meeting diagnostic criteria for major depressive disorder (as determined by the MINI, per protocol) decreased from baseline to 9 weeks but the difference between Deprexis and control was not statistically significant (p=0.079; appendix A). On the basis of the MINI analysis, the number needed to treat was three.

When assessing quality of life, as measured by the WHO-QoL BREF, we saw a treatment difference only in the psychological wellbeing subscale (table 2). When assessing the Fatigue Scale For Motor and Cognitive Function (FSMC), we saw improvement with intervention versus control in only the motor fatigue subscale (table 2) but not on cognitive fatigue symptoms (table 2). We saw no difference in any of the disease-specific quality-of-life (HAQUAMS) subscales (table 2).

**Figure 3: Effects of Deprexis on dichotomised Beck Depression Inventory (BDI)** Patients were grouped as either below the cutoff for clinical depression (BDI score 0–13) or with scores indicative of clinical depression (BDI score >13).

On average, patients allocated to the Deprexis group spent 332 min (about 5.5 h) working with the programme (median 310 min; range 50–905). Patient satisfaction with the programme was high and most participants reported that the intervention met or exceeded their expectations (appendix A). Additionally, many of the participants indicated that they would recommend Deprexis to others with mild-to-moderate depression and especially those with multiple sclerosis. Only a few participants indicated that they needed assistance in handling the programme (n=6, 17%). However, about three-quarters (n=27, 77%) of the participants stated that they had to force themselves to complete all the sessions, and more than half (n=18, 51%) suggested that the programme might require some adjustments to suit the needs of patients with multiple sclerosis.

None of the enrolled participants met the predefined criterion for acute risk of suicide (response



3a or 3b on SBQ-R item 3 plus score of 5 or 6 on SBQ-R item 4) at baseline or the 9-week assessment. For the low-threshold definition using BDI item 9, the criterion was not met by any patient in the Deprexis group (baseline n=0; 9 weeks n=0) but was met in one instance in the control group (n=1; n=1). For SBQ-R item 4, two patients met the low-threshold criterion at baseline and no patients met it at week 9 in the Deprexis group. In the control group, four patients met this criterion at both baseline and 9 weeks. However, using the low-threshold criteria, we saw no evidence of new occurrences of suicidal ideation during the trial in either group. We saw worsening of depressive symptoms during the trial from below to above the cutoff for caseness (BDI >13) in three patients in the control group but none in the Deprexis group.

All 35 patients assigned to Deprexis and included in the 9-week analysis also completed the 6-months' follow-up examination. At 6 months, BDI scores in these participants were lower than at baseline (mean BDI at baseline 19.37 [SD 9.59]; mean BDI at 6 months 14.80 [10.03]; p=0.001).

## Articles

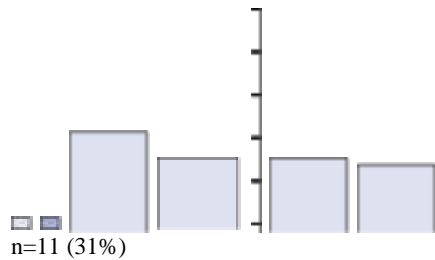
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BDI score 0–13

BDI score >13 100

80 60 40 20

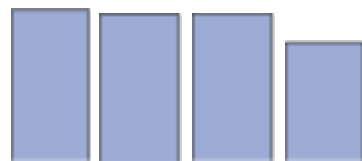
0



n=16 (46%)

n=12 (33%)

n=11 (31%)



n=24 (69%)

n=19 (54%)

n=24 (67%)

n=25 (69%)

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Baseline Deprexis

9 weeks

Baseline

9 weeks

Control

Proportion of participants (%)

## Articles

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### **Panel: Research in context**

#### **Systematic review**

We searched Pubmed for relevant studies using the search terms “depress\* AND multiple sclerosis AND (intern\* OR comput\*) AND (therap\* OR intervention OR treatment)”. The search was restricted to English or German publications and carried out in April 2012, without date restrictions. We also browsed reference lists of relevant papers and our own libraries. We retrieved 80 articles, eight of which described trials of interventions in multiple sclerosis. Of these, two described internet-based interventions in multiple sclerosis (one uncontrolled study and one small randomised trial targeting fatigue in multiple sclerosis). Thus, we concluded that a phase 2 randomised controlled trial of an internet-based intervention for depression in multiple sclerosis was warranted.

#### **Interpretation**

Our findings show that a fully automated, internet-based cognitive behavioural therapy (CBT) intervention is feasible and effective in patients with multiple sclerosis and self-reported depressive symptoms, adding to evidence that CBT is an effective treatment strategy in multiple-sclerosis-associated depression. The ability to provide patients with a self-guided, remote-access CBT intervention as shown in this trial provides new evidence that increases the range of therapeutic options available to such patients, at least as an interim solution until psychotherapy is available. Such options might be particularly relevant for patients with mobility or cognitive problems as well as pronounced fatigue, which could affect their ability to regularly attend sessions with a therapist. Furthermore, it offers patients who do not live close to care centres a low-barrier access to treatment. In times of increasingly restricted health-management costs, such online CBT interventions might offer a cost-effective approach.

#### **Discussion**

We saw reduced depression scores, as measured by the BDI, in patients with multiple sclerosis participating in a 9-week iCBT intervention (Deprexis) compared with those not participating in

the intervention. Importantly, Deprexis not only reduced severity of depressive symptoms, but also increased quality of life and decreased fatigue, adding to the clinical relevance of the findings.

Our results are in accordance with the positive findings reported in a recent, non-controlled pilot study on the feasibility of an online problem-solving programme in multiple sclerosis.<sup>30</sup> Our results are also in line with randomised trials done in otherwise healthy patients with depression and without comorbid somatic disorders, which lends support to the usefulness of iCBT in general<sup>31</sup> and specifically the Deprexis programme in patients with major depressive disorder.<sup>18,32,33</sup>

Few randomised trials have assessed the effects of pharmacological or behavioural interventions to treat depression in patients with multiple sclerosis. Findings from studies using antidepressant pharmacotherapy in this population have suggested some efficacy but also indicated frequent side-effects.<sup>13</sup> CBT-based psychotherapy in group or individual settings is effective in reducing depressive symptoms in multiple sclerosis.<sup>14</sup> Moreover, CBT administered by telephone has shown promising results.<sup>16</sup> Although this approach eliminates the need for the patient to travel, it still requires availability of a trained psychotherapist. In view of the motor impairment and

fatigability typically associated with multiple sclerosis, as well as the limited availability of psychotherapists, self-guided, automated, internet-based interventions such as Deprexis might be particularly useful for patients with multiple sclerosis and a need for depression treatment, at least as an interim solution until psychotherapy is available. Another obvious advantage of Deprexis and similar interventions is that they can be broken down into smaller modules and completed at any time, therefore allowing patients with increased fatigability or deficits in cognitive domains such as processing speed or attention to proceed at their own pace. Overall, retrospective, subjective ratings lend support to the feasibility and acceptance of Deprexis by patients with multiple sclerosis (appendix A).

Findings from a meta-analysis of iCBT interventions show that guided iCBT is more effective than self-guided treatments and that even a small degree of contact with a clinician (eg, an interview or coming to the hospital for assessments) will lead to better outcomes.<sup>34</sup> That the effect size seen in the present study in a subgroup of patients undergoing psychodiagnostic assessment at our outpatient centre was larger than in the whole sample is in line with this possibility. Evidence has suggested that adding short face-to-face consultations in a blended-care design can have positive effects on retention and outcome of iCBT.<sup>19</sup> Email support might also be useful.<sup>33</sup> Therefore, the efficacy of interventions such as Deprexis in multiple sclerosis might be further enhanced by adding therapist support in one form or another. Whether or not this is indeed beneficial remains to be tested in future studies and is an active area of investigation in our research.

Our study had some limitations. We selected participants on the basis of self-reported

depressive symptoms. A clinical diagnosis of major depressive disorder was not required for enrolment, which could have resulted in mild to moderate levels of depressive symptoms in participants. A previous study of Deprexis has reported strongest effects in patients suffering from moderate depressive symptoms.<sup>32</sup> Assessments of Deprexis in more severe depression in general and in multiple sclerosis specifically are absent. Overall, the group differences in our study were slightly smaller than the one reported before in patients with depression but no comorbid somatic disorder.<sup>18</sup> This finding might be due to the lower level of depressive symptoms at baseline in our study. Alternatively, it could show the need to adjust Deprexis to multiple-sclerosis-specific needs, as indicated by the retrospective appraisal of the programme in our patients. The drop-out rate in our study was just above the cutoff for class-I evidence although within the range typically seen in behavioural interventions<sup>35</sup> and low compared with other online interventions.<sup>36</sup> Adherence to an online programme, though, is difficult to predict.<sup>37</sup> Furthermore, the sample size was small, particularly in the clinical subgroup analyses. It remains to be seen if Deprexis effects can be maintained when implemented at a larger scale outside of clinical trials.

This interventional study provides class-II evidence for the efficacy of an internet-based CBT intervention (Deprexis) for the treatment of depressive symptoms in patients with multiple sclerosis.<sup>38</sup> This finding increases therapeutic options for depression associated with multiple sclerosis and might help to overcome treatment barriers such as mobility problems often encountered by patients with multiple sclerosis and other chronic health conditions (panel).

#### **Contributors**

AF, JS, CH, SM, and SMG designed the study. AF, JS, and SL obtained the data. AF, JS, EV, JP, OTW, CH, SM, and SMG did the analysis and interpretation of data. AF and SMG drafted the paper. JS, EV, OTW, JP, SL, CH, and SM revised the paper for intellectual content.

#### **Declaration of interests**

SMG reports personal fees from Novartis. All other authors declare no competing interests.

#### **Acknowledgments**

The research leading to these results has received funding from the European Union Seventh Framework Program (FP7/2007-2013) under grant agreement n°[268381]. SMG is supported by a Heisenberg Fellowship from the Deutsche Forschungsgemeinschaft (DFG, GO1357/4-1 and 5-1).

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