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ARTICLE



# Creation and validation of a linear index to measure the health state of patients with depression in automated healthcare databases

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**ABSTRACT**

**Background and objective**: We previously built a weighted Depressive Health State Index (DHSI) based on 29 parameters routinely collected in an automated healthcare database (AHDB). We now propose a linear DHSI (L-DHSI) which is easier to use and to replicate across AHDBs.

**Methods**: A historical cohort of patients with ≥1 episode of depression was identified in the Clinical Practice Research Datalink (CPRD). The DHSI was calculated for each treated episode of depression. Validation was performed by using validated definitions of remission (proxy and Patient Health Questionnaire 9 or PHQ-9) and comparing the L-DHSI between subgroups. Reliability was assessed using Cronbach's alpha.

**Results**: Between 1 January 2006 and 31 December 2012, 309,279 episodes of depression were identified in the CPRD. Remission was observed in 5% of the patients with lowest L-DHSI scores and in 78% of the patients with highest L-DHSI scores. Although less sensitive than the weighted DHSI, the L-DHSI was reliable and relatively easy of use. The L-DHSI was highly correlated to the weighted DHSI (Spearman coefficient 0.790, $p < 0.001$).

**Conclusion**: The L-DHSI represents a good balance between reliability, usability, and reproducibility. In addition, the linearity of this index allows for an easier interpretation than the original weighted DHSI.

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## Introduction

The assessment of the effectiveness of drugs in real-life settings is an essential part of health-related studies. For these studies, the use of automated healthcare databases (AHDB) is increasing and has some advantages including large sample sizes and limited participation biases [1]. Nonetheless, AHDBs often lack detailed clinical data and require the use of proxies that do not always provide sufficient granularity [2,3]. In studies related to major depressive disorder (MDD), remission status based on prescription patterns is a proxy often used to try to overcome this lack of clinical data. In addition, a major issue of using remission as a real-life effectiveness outcome is its binary characteristics (i.e. remission vs. non-remission) that does not reflect the complexity of the patients' health state in MDD [4].

To have a more precise estimation of health state of patients with depression using the data contained in AHDBs, a depression health state index (DHSI) was created [5]. A unique index was created by combining all variables available in an AHDB and considered to be related to the health state of patients with depression. Weights were attributed to the selected variables by expert inputs based on the different impact that the variables were thought to have on patient's health state. Parameters and weights were defined and attributed by a group of four experts, and a previous publication has shown that this DHSI is robust to individual parameter modifications and specific of depression severity [6].

A survey was conducted in 41 general practitioners and 32 psychiatrists in the UK to confirm the initial choice of parameters and weights [7]. Most physicians were in agreement with the relevance of the selected parameters and their polarity (i.e. positive or negative) on the health state of patients with depression (reliability: Cronbach's alpha >0.80). However, poor agreement was observed between the initial weights attributed through expert input and the weights attributed by the physicians in the survey, especially for low-weight parameters.

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One of the initial aims of the DHSI was to build a reliable index of the health state of patients with depression and to propose a methodology that would be replicable in any AHDB. In view of the non-negligible amount of work required to build a weighted DHSI and the challenge represented by the attribution of weights to the parameters, we developed an alternative, linear version of the DHSI (L-DHSI) in which parameters would only differ in polarity (i.e. weights of +1 or −1).

We here describe the development and validation of this L-DHSI in the Clinical Practice Research Datalink (CPRD) and we discuss its difference with the original weighted DHSI.

## Methods

The detailed methods used to create the DHSI, and initial results and validation have been published previously by the same research group [5,6].

### *Study design*

As detailed in the methodological manuscript [5], the study is based on a historical cohort design using data from the CPRD. The CPRD is a database of anonymized primary care records for patients registered at general practices in the UK. It covers approximately 8% of the UK population and includes information on the prescription of medicines, referral to hospitals or specialists, and diagnoses entered by the general practitioner (GP) using the Read or Oxford Medical Information System codes. This widely used database has been validated for pharmacoepidemiological studies [8–10].

### *Study population*

For this study, the same dataset and the same population as for the weighted DHSI was used [5,6]. Patients with at least one depressive episode during the study period (1 January 2006–31 December 2012) were included.

Patients were selected based on the following inclusion criteria (Figure 1):

- incident prescription of antidepressant (AD) monotherapy during the study period (defined as index date),
- no AD prescription within the 6 months prior to index date,
- incident diagnosis of depression during the 61 days preceding or following the index date,
- patients aged 18 or older at index date,
- at least 6 months of available data before index date,
- at least 9 months of available data following index date (except for patients with a recorded death during this period).

Exclusion criteria were a lifetime diagnosis of either bipolar disorder or schizophrenia.

Each segment of a patient's data meeting the selection criteria was defined as a 'depressive episode', thus several depressive episodes could be observed for each patient included in the study. The end of a depressive episode was the end of an AD prescription without any other AD prescription during the following 182 days, or the end of the patient's follow-up in the database (censoring) whichever came first. Baseline characteristics for each depressive episode were collected between 5 months before and 1 month after the index date (defined as reference period). The events used to derive the parameters included in the DHSI were considered in a time window starting 3 months after index date and up to 9 months after index date (defined as follow-up period) (Figure 1). This time span is usually considered to assess remission for a patient with depression in routine clinical practice [11]. Some parameters were defined relative to baseline characteristics (e.g. dose augmentation).

The study protocol was reviewed and approved by the CPRD review committee (ISAC protocol number: 13_182).

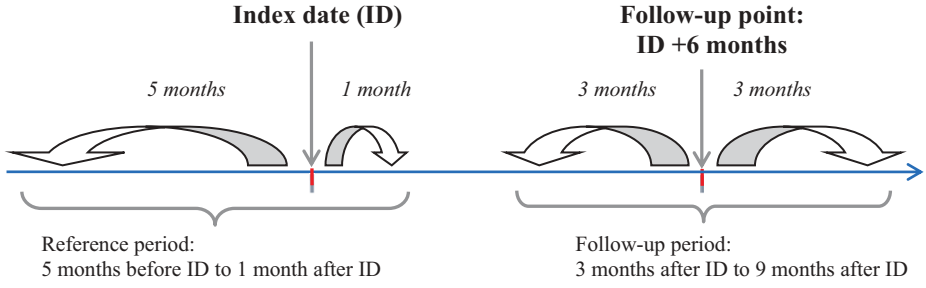


Figure 1. Study design (Illustration from [5]).
The index date was the date of the first prescription of antidepressant for a patient meeting the inclusion and exclusion criteria in the database.

### Creation of the linear DHSI

The L-DHSI is a score comprised of the same 29 different parameters (i.e. existing variables or derived from existing variables) as considered for the initial DHSI (Table 1) [5,6]. These parameters were defined and selected by a group of four clinical and methodological experts among the variables available in the CPRD. Each parameter was classified according to its presupposed positive or negative polarity on the depressive health state of the patient. The occurrence of a positive parameter would lead to the addition of 1 point to the overall score and the occurrence of a negative parameter would lead to the suppression of 1 point to the overall score. All parameters only contributed in direction and no more than 1 point could be accounted for each individual parameter, even if the same parameter had occurred several times (e.g. hospitalization). Absent parameters did not contribute to the score. To make the interpretation of the score easier, the score obtained for the different depressive episodes was translated from the initial [−19;10] range to the final [0–29] range, where 0 was considered the worst health state possible and 29 the best health state possible.

## Statistical analyses

### Descriptive analyses

The L-DHSI was summarized using mean, standard deviation (SD), minimum, maximum, median and first and third quartiles. It was described overall and across geographic regions of the UK, age groups and gender.

A principal component analysis (PCA) to examine the structure of the L-DHSI was also conducted.

### Validation of the L-DHSI

Validation was performed using two different sets of analyses: i) by describing patients' remission status based on proxies for this outcome according to deciles of the L-DHSI, and ii) by comparing the mean L-DHSI scores of population subgroups known to represent different severities of depression.

i) The proportion of patients in remission per deciles of the L-DHSI was examined using two different definitions for remission: a previously validated proxy based on treatment patterns [3] and a proxy based on the Patient Health Questionnaire 9 (PHQ-9) score when available for a depressive episode [12].

Remission based on treatment patterns was defined as an AD treatment discontinuation >45 days during a depressive episode. Other clinical outcomes were defined as follows: relapse was defined as an interruption of >45 days of the antidepressant prescriptions and a new prescription of any psychotropic drug <180 days after the last antidepressant prescription. Remission without relapse was an interruption of >45 days of antidepressant prescription with no further psychotropic prescriptions during follow-up period. This definition demonstrated an acceptable level of concordance between remission obtained from the computerized databases and clinical criteria [3].

Remission according to the PHQ-9 values available in the CPRD, as recorded by GPs, was defined according to PHQ-9 validated cut-off, which classified remission as a PHQ-9 value ≤4 using the last available value during the follow-up period of a specific depressive episode (Figure 1).

These analyses were purely descriptive and no statistical tests were used.

ii) The second set of validation analyses consisted in the comparison of L-DHSI scores among subgroups expected to differ in terms of depression severity: antipsychotic augmentation (yes/no) during the depressive episode, psychiatric hospitalisation (yes/no) during the depressive episode, any hospitalisation (psychiatric and other) (yes/no) during the depressive episode and remission status according to PHQ-9 (yes/no). Statistical testing for these analyses is described below.

### Reliability of the L-DHSI

Reliability of the index was tested using the Cronbach's alpha [13] The Cronbach's alpha was also calculated after removal of one of the parameters from the L-DHSI. The L-DHSI was recalculated after each modification and the item-total correlations were performed.

### Correlation between the weighted DHSI and the L-DHSI

Spearman correlation was also performed between the original weighed DHSI and the L-DHSI.

### Statistical tests

Statistical comparisons were performed using non-parametric tests: the Wilcoxon-Mann-Whitney test for binary variables and the Kruskal–Wallis test for variables with three or more levels. Due to the large number of depressive episodes included in the study, statistical significance could be reached for small, and potentially non-clinically meaningful differences. To take these potential artefacts into account, an effect size was also calculated and considered for interpretation of the results. Effect size for L-DHSI differences between groups was computed as follows: (mean group x – mean group y)/SD of mean group y. As we report here the first statistical results for the L-DHSI, the thresholds of clinical relevance are unknown for this index. Therefore, the interpretation of effect size was based on Cohen's conventions: ≤0.2: no

**Table 1.** Parameters included in the L-DHSI and their relative polarity.

| Parameter | Definition | Polarity |
|---|---|---|
| No antidepressant prescriptions[a] | At least 2 consecutive visits without any prescription for an antidepressant during follow-up period and no ulterior psychiatric prescription during follow-up. | Positive |
| No psychiatric co-prescriptions[a] | At least 2 consecutive visits without any prescription for any psychiatric co-prescription during follow-up period and no ulterior psychiatric prescription during follow-up. | Positive |
| Increasing duration between visits to the GP[b] | Duration between to visits to the physician during follow-up period is one standard deviation or more above the duration observed during follow-up period. | Positive |
| Decreasing N of other psychiatric co-prescription[b] | A lower number of distinct molecules of psychiatric drugs (other than hypnotics) during follow-up period when compared to reference period (no threshold). | Positive |
| Disappearance of depression diagnoses[a] | At least one depression diagnostic code during follow-up period but none at last visit(s) | Positive |
| Decreasing N of somatic co-morbidities[b] | A lower number of distinct somatic comorbidities during follow-up period when compared to reference period (no threshold). | Positive |
| Decreasing N of hypnotic co-prescription[b] | A lower number of prescriptions of hypnotic drugs during follow-up period when compared to reference period (no threshold). | Positive |
| Decreasing N of somatic co-prescription[b] | A lower number of prescriptions of somatic drugs during follow-up period when compared to reference period (no threshold). | Positive |
| Pregnancy[a] | Single incident pregnancy recorded during the follow-up period (excluding deliveries and pregnancies leading to voluntary terminations) | Positive |
| Dose decrease of initial treatment[b] | For patients whose AD molecule is not modified between reference and follow-up periods: the mean daily dose of the complete follow-up period is lower than the mean daily dose of the last month of reference period (no threshold) | Positive |
| Death of the patient[a, c] | Single incident recorded death of the patient during follow-up period | Negative |
| Psychiatric hospitalisation[a] | Single incident recorded psychiatric hospitalisation of the patient during follow-up period | Negative |
| Suicide attempt[a] | Single incident recorded suicide attempt of the patient during follow-up period | Negative |
| ECT prescription[a] | Single incident recorded ECT prescription during follow-up period | Negative |
| Referral to a psychiatrist[a] | Single incident recorded psychiatrist referral or visit to a psychiatrist during follow-up period | Negative |
| Sick-leave[a, c] | Single incident recorded sick leave prescription during follow-up period | Negative |
| Switch[a] | The prescription of a different AD prescribed between 31 days before and 183 days after the initial AD has been stopped. The first AD stop can occur before the follow-up period but new prescription must occur during follow-up period | Negative |
| Early termination of pregnancy[a, c] | Single incident termination of pregnancy during the follow-up period | Negative |
| Increasing N of other psychiatric co-prescriptions[b] | A higher number of distinct molecules of psychiatric drugs (other than hypnotics) during follow-up period when compared to reference period (no threshold). | Negative |
| Appearance of a new psychiatric comorbidity[a] | Single incident appearance of a psychiatric comorbidity during follow-up period that is not present at reference period. | Negative |
| Combination (AD co-prescription)[a] | The prescription of a different AD than the initial AD any time between the first day after index date and no later than 31 days before the initial AD has been stopped. New prescription can occur at any time after index date but the concomitance of treatment must be observed during follow-up period | Negative |
| Augmentation (AP co-prescription)[a] | The prescription of an antipsychotic or lithium that appears any time between the 1st day after index date and no later than 31 days before any AD treatment has been stopped. New prescription can occur at any time after index date but the concomitance of treatment must be observed during follow-up period. | Negative |
| Relapse/Recurrence type event[a] | Any prescription for any psychiatric treatment during the follow-up period between 45 and 183 days after previous AD stop. The new prescription must occur during follow-up period, but the first AD stop can occur before follow-up period | Negative |
| Decreased duration between visits to the GP[b] | Duration between to visits to the physician during follow-up period is one standard deviation or more below the duration observed during follow-up period. | Negative |
| Dose increase of the initial treatment[b] | For patients whose AD molecule is not modified between reference and follow-up periods: the mean daily dose of the complete follow-up period is higher than the mean daily dose of the last month of reference period (no threshold) | Negative |
| Increasing N of somatic co-morbidities[b] | A higher number of distinct somatic comorbidities during follow-up period when compared to reference period (no threshold). | Negative |
| Increasing N of hypnotic co-prescriptions[b] | A higher number of prescriptions of hypnotic drugs during follow-up period when compared to reference period (no threshold). | Negative |
| Increasing N of somatic co-prescriptions[b] | A higher number of prescriptions of somatic drugs during follow-up period when compared to reference period (no threshold). | Negative |
| Hospitalisation for other causes[a] | Single incident recorded non psychiatric hospitalisation of the patient during follow-up period | Negative |

[a]Parameter measured in the follow-up period only; [b]Parameter measured relatively to the reference period; [c]All cause
AD: Antidepressant; AP: Antipsychotic; ECT: Electroconvulsive therapy; GP: General Practitioner; N: Number.

effect; between >0.2 and ≤0.5: small effect size; between >0.5 and ≤0.8: moderate effect size; >0.8: large effect size [14]. All statistical analyses were performed using the R-software.

## Results

### Description of the L-DHSI

A total of 309,279 episodes of depression (273,346 patients) were identified in the CPRD from 1 January 2006 to 31 December 2012. The mean ± SD L-DHSI score was 20.3 ± 2.2 (Table 2). Over a theoretical range of 0–29, minimum was 10, first quartile was 19, median was 21, third quartile was 22 and maximum was 28. The distribution of L-DHSI scores were close to a normal distribution (Figure 2).

The mean L-DHSI scores slightly decreased across age groups and ranged from 20.7 ± 2.1 in the 18–29 year age group to 19.8 ± 2.3 in the ≥80 years age group (Table 2). This was associated to a small effect size (<0.4). No significant difference was observed between males and females or across geographical regions.

Principal component analysis showed that 11 factors had an eigenvalue above 1, including two factors that had an eigenvalue above 1.9 (Figure 4). Most of the other factors had values close to 1.

### Validation of the DHSI

Based on the treatment pattern definition of remission and relapse, higher scores of the L-DHSI were associated with greater proportions of episodes with remission (from 5% in the first decile to 78% in the tenth decile). In parallel, we observed lower proportions of episodes with relapse with higher L-DHSI scores (from 39% in the first decile to 4% in the tenth decile) or non-remission (from 57% in the first decile to 18% in the tenth decile) (Figure 3).

Validation was also performed using the remission status according to PHQ-9 (Table 3). A total of 15,392 episodes (5% of all included episodes) had an analysable PHQ-9 score available during follow-up. The proportion of remissions observed according to PHQ-9 increased with increasing deciles of the L-DHSI.

Known group validation was based on the hypothesis that prescription of an antipsychotic or hospitalization indicates a worse depressive state. Comparison of L-DHSI scores among these predefined groups showed significantly lower scores in patients with versus without somatic hospitalization (p<0.001, effect size = 0.67), psychiatric hospitalization (p<0.001, effect size = 0.92) or antipsychotic augmentation (p<0.001, effect size = 1.72) (Table 4).

### Reliability

Reliability of the L-DHSI was analyzed using the Cronbach's alpha (or tau-equivalent reliability) (Table 5). The overall Cronbach's alpha was 0.440. Removal of a parameter from the L-DHSI was associated with Cronbach's alphas ranging from 0.367 for 'Increasing number of somatic co-prescriptions' to 0.480 for 'Disappearance of depression diagnosis'.

Usefulness of the parameters initially included in the L-DHSI was further studied using the item-total correlations (Table 5). This was an indicator of the 'amount of information' contained in the parameter that is already brought to the L-DHSI by one or several of the other parameters. The value of Spearman's coefficients ranged from −0.533 for 'Increasing number of somatic co-prescription' to 0.494 for 'Decreasing number of somatic co-prescription'.

Table 2. Description of the L-DHSI according to patient characteristics.

| | | L-DHSI score | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Mean ± SD | Min | Q1 | Median | Q3 | Max | p value | Effect size |
| **All episodes** | **309,279** | **20.3 ± 2.2** | **10** | **19** | **21** | **22** | **28** | | |
| **Age group** (years) | | | | | | | | <0.001[a] | |
| 18–29 | 66,588 | 20.7 ± 2.1 | 10 | 19 | 21 | 22 | 28 | | |
| 30–49 | 141,697 | 20.4 ± 2.2 | 10 | 19 | 21 | 22 | 27 | | −0.14 |
| 50–69 | 74,999 | 20.2 ± 2.2 | 10 | 19 | 20 | 22 | 27 | | −0.23 |
| 70–79 | 15,812 | 20.0 ± 2.3 | 10 | 18 | 20 | 22 | 27 | | −0.32 |
| ≥80 | 10,183 | 19.8 ± 2.3 | 10 | 18 | 20 | 21 | 27 | | −0.39 |
| **Gender** | | | | | | | | 0.186[b] | 0.00 |
| Male | 103,003 | 20.4 ± 2.1 | 10 | 19 | 21 | 22 | 28 | | |
| Female | 206,275 | 20.3 ± 2.2 | 10 | 19 | 20 | 22 | 27 | | |
| **Geographical region** | | | | | | | | <0.001[a] | <0.2 |
| England | 232,624 | 20.4 ± 2.2 | 10 | 19 | 21 | 22 | 27 | | |
| N. Ireland | 10,888 | 20.0 ± 2.4 | 10 | 18 | 20 | 22 | 27 | | −0.19 |
| Scotland | 36,766 | 20.4 ± 2.2 | 10 | 19 | 21 | 22 | 28 | | 0.03 |
| Wales | 29,001 | 20.1 ± 2.2 | 10 | 19 | 20 | 22 | 27 | | −0.12 |

[a]Kruskal–Wallis test; [b]Wilcoxon-Mann-Whitney test

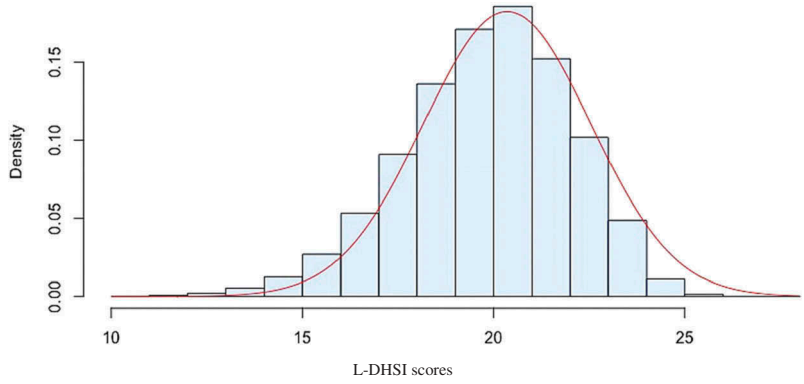


Figure 2. Density histogram of the L-DHSI.

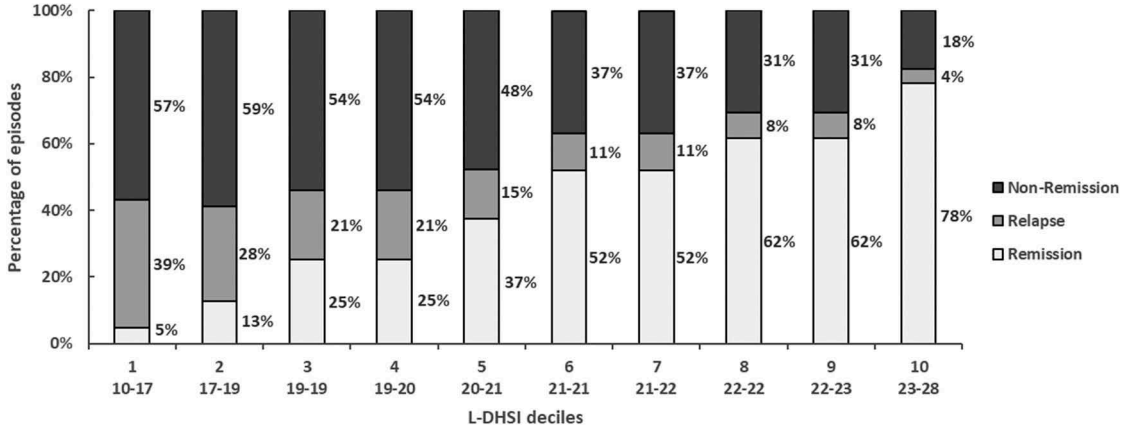


Figure 3. Distribution of episodes according remission, non-remission or relapse status across L-DHSI deciles.

Relapse: interruption of >45 days of the antidepressant prescriptions and a psychiatric prescription is made <180 days after last antidepressant prescription; Remission non-relapse: interruption of >45 days of antidepressant prescription with no further psychiatric prescriptions during episode follow-up

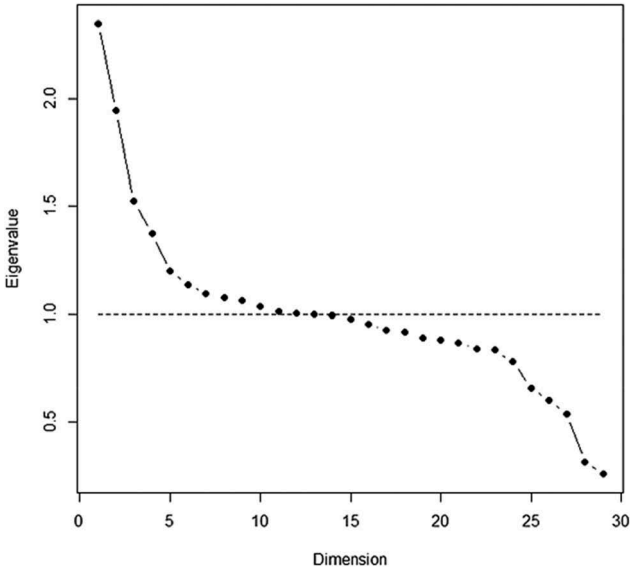


Figure 4. Scree plot for the principal component analysis of the L-DHSI.

### *Correlation between the weighted DHSI and the L-DHSI*

Spearman's correlation between the L-DHSI and the weighted DHSI showed high correlation between both indexes (Spearman coefficient 0.790, $p<0.001$).

## Discussion

The weighted DHSI was designed as a reliable and continuous index of the health state of patients with depression. The L-DHSI was built on this original research to create an alternative tool that would be easier to use and to replicate. The L-DHSI was shown to be less sensitive than the weighted DHSI but results showed acceptable reliability with respect to a simplification of the methodology to build this index.

We first developed the DHSI (referred as 'weighted DHSI' in the manuscript) to address the current lack of an indicator that could provide a continuous evaluation

**Table 3.** Remission according to PHQ-9 scores across deciles of L-DHSI (N = 15,392).

| | Deciles of the L-DHSI | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| PHQ-9 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Remission | 5.7% | 9.8% | 11.5% | 11.5% | 13.8% | 15.3% | 15.3% | 15.5% | 15.5% | 15.8% |
| Non-remission | 94.3% | 90.2% | 88.5% | 88.5% | 86.2% | 84.7% | 84.7% | 84.5% | 84.5% | 84.2% |

**Table 4.** Comparisons of L-DHSI scores across pre-defined subgroups.

| | | L-DHSI score | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | Mean ± SD | Min | Q1 | Median | Q3 | Max | p-Value[c] | Effect size |
| **All episodes** | **309,279** | **20.3 ± 2.2** | **10** | **19** | **21** | **22** | **28** | | |
| **Antipsychotic augmentation[a]** | | | | | | | | <0.001 | |
| Augmentation | 3,663 | 16.7 ± 2.2 | 10 | 15 | 17 | 18 | 23 | | |
| No augmentation | 305,616 | 20.4 ± 2.1 | 10 | 19 | 21 | 22 | 28 | | 1.72 |
| **Any hospitalization[b]** | | | | | | | | <0.001 | |
| Yes | 75,225 | 19.2 ± 2.3 | 10 | 18 | 19 | 21 | 26 | | |
| No | 234,054 | 20.7 ± 2.0 | 11 | 19 | 21 | 22 | 28 | | 0.67 |
| **Psychiatric hospitalization[b]** | | | | | | | | <0.001 | |
| Yes | 8,495 | 18.2 ± 2.4 | 10 | 17 | 18 | 20 | 26 | | |
| No | 300,784 | 20.4 ± 2.1 | 10 | 19 | 21 | 22 | 28 | | 0.92 |

[a]Augmentation defined as a prescription of an antipsychotic drug concomitant to antidepressant prescription; [b] during depressive episode; [c] Wilcoxon-Mann-Whitney tests.

**Table 5.** Cronbach's Alpha for L-DHSI following the removal of a parameter, and item-total correlations.

| Removed parameter | Value of the parameter | Item-total Correlations | Cronbach's Alpha |
|---|---|---|---|
| **None** | | **1** | **0.440** |
| Disappearance of depression diagnoses | +1 | 0.000 | 0.480 |
| Disappearance of AD prescription | +1 | 0.249 | 0.459 |
| Decreasing duration between GP visits | −1 | −0.110 | 0.449 |
| Increasing duration between GP visits | +1 | 0.138 | 0.446 |
| Decreasing N of hypnotic co-prescriptions | +1 | 0.160 | 0.444 |
| Decreasing N of AP co-prescriptions | +1 | 0.151 | 0.444 |
| Incident pregnancy | +1 | 0.063 | 0.443 |
| Pregnancy early termination | −1 | −0.017 | 0.442 |
| ECT prescription | −1 | −0.012 | 0.441 |
| Death of patient | −1 | −0.015 | 0.441 |
| Suicide attempt | −1 | −0.023 | 0.441 |
| Sick-leave | −1 | −0.034 | 0.441 |
| Incident AD combination | −1 | −0.122 | 0.438 |
| Hospitalization for other causes | −1 | −0.276 | 0.438 |
| Psychiatric hospitalization | −1 | −0.166 | 0.436 |
| Switch | −1 | −0.175 | 0.435 |
| Incident AP co-prescription | −1 | −0.183 | 0.434 |
| Dose increase of any AD treatment | −1 | −0.198 | 0.434 |
| Referral to a psychiatrist | −1 | −0.292 | 0.433 |
| Dose decrease of initial treatment | +1 | 0.343 | 0.432 |
| New psychiatric co-morbidity | −1 | −0.245 | 0.428 |
| Relapse/recurrence of any event | −1 | −0.339 | 0.424 |
| Increasing N of hypnotic co-prescription | −1 | −0.284 | 0.423 |
| Increasing N of AP co-prescription | −1 | −0.352 | 0.414 |
| Decreasing N of somatic co-morbidity | +1 | 0.399 | 0.411 |
| No AP co-prescription | +1 | 0.391 | 0.405 |
| Increasing N of somatic co-morbidity | −1 | −0.445 | 0.394 |
| Decreasing N of somatic co-prescription | +1 | 0.494 | 0.381 |
| Increasing N of somatic co-prescription | −1 | −0.533 | 0.367 |

AD: antidepressant; AP: antipsychotic or lithium; ECT: Electroconvulsive therapy; GP: general practitioner; N: number.

of the health state of patients with depression from AHDBs [5,6]. In its initial shape, the DHSI was built with the same parameters as used in the present L-DHSI but these parameters were weighted to quantify the respective impact of each parameter on the depressive health state beyond its polarity. The weighted DHSI proved to be sensitive and robust. However, an important amount of preliminary work to define the weights for each parameter is required and may jeopardize an easy use by other research teams and/or implementation into other AHDBs. In addition, the survey that was conducted in 41 general practitioners and 32

psychiatrists in the UK showed that physicians generally agreed with the selected parameters and their polarity but disagreed with the attributed weights [7].

To obtain an index that would remain specific and that would keep the overall properties and objective of the weighted DHSI, but that would be easier to implement in different AHDBs, we decided to simplify weighting and apply a binary value (i.e. −1 or +1). This value reflects the positive or negative impact of each parameter on the patient's health state. It was anticipated that such a simplification of the index would be associated with decreased reliability. This was confirmed by low Cronbach's alphas (i.e. <0.5). Reliable Cronbach's alphas are usually expected to be above 0.6. However, high Cronbach's alphas were not expected for the L-DHSI: this index was not built within a usual psychometric paradigm where items would have been purposely built. 'Depression' is a complex concept and the L-DHSI uses existing variables from databases that were selected as they were considered to be indicators of the health state of patients with depression. As indicated by the differences in L-DHSI scores between patients with or without antipsychotic augmentation, any hospitalization or psychiatric hospitalization, the L-DHSI appears specific of the health state of patients with depression. Nevertheless, all the variables included in the L-DHSI are considered to measure very different aspects of the health state related to depression. When performing the PCA, it was found that most of the values were around 1 indicating that the L-DHSI includes different factors that are independent from each other and each representing specific aspects of depression. In addition, the item-total correlations provided results that are consistent with those of Cronbach's alpha. The item-total correlation coefficients were always inferior to 0.5. An index where the item-total correlation coefficients would be close to 1 would indicate that the data contained in the index would be redundant with the data contained in the removed parameter. On the contrary, the low coefficients we observed suggest that the index considers very different aspects of depression. Item-total correlations can also help identifying which variable is more specific of depression. Nonetheless, variations in the Cronbach's alpha and item-total correlations depend on the prevalence of the variable. This can explain why variables like suicide attempts, ECT (which are low incidence events, and may further be under-reported in the CPRD where the data is generated in general practitioner practices) show low item-total correlations and low variation of the Cronbach's alpha following their removal from the index. Refined analyse of the usefulness of each variable in the model would require deeper analyses taking prevalence into account.

Qualitative comparisons between the weighted DHSI and the L-DHSI suggest that the latter has a reduced sensitivity to very severe events for patients with depression. For instance, the observed effect size was lower for psychiatric hospitalizations in the L-DHSI than in the weighted DHSI (0.9 vs 1.7). Using equal weights was further associated with a reduction of the range in the L-DHSI, which lowered granularity in the description and classification of patients with depression. However, although the L-DHSI is less sensitive to severe events related to depression than the weighted DHSI, both remain highly correlated. The main advantage of the L-DHSI is that it a faster and simpler implementation into other databases and settings as it only requires the identification of relevant parameters. Because of the linear relationship between the presence of a parameter and the score, it is also easier to interpret. Due to its easy implementation in AHDB, the L-DHSI can be used by pharmacoepidemiology researchers (e.g. by healthcare payers, the pharmaceutical industry or outcomes researchers) as a hypothesis generation tool in context of measuring the effectiveness of antidepressant therapy in patients suffering from depression. The original DHSI [5,6] which is more complex to implement but also more sensitive than the L-DHSI, could be used to conduct research on outcomes (e.g. comparative effectiveness research) following initial analyses with the L-DHSI.

Limitations of the L-DHSI are inherent to the construction of this type of indexes and are similar to those listed for the original DHSI [5,6]. The parameters included highly depend on the database. Its implementation into another database would require a similar thorough selection of pertinent parameters. And even in this case results may differ. This could be due to different settings; the data contained in the CPRD are collected among general practitioners. Differences may also relate to the available parameters themselves and their methods of collection.

In conclusion, the L-DHSI is characterised by a good balance between the ability to capture the health state of patients with depression in AHDBs and the usability and reproducibility from a practical perspective. Because of the linear relationship between the presence of a parameter and the score, it is also easier to interpret than the original weighted DHSI. It represents a reliable alternative between the usual binary estimates of the patient's health state and the more complex weighted DHSI.

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## Conflict of interest statement

Maëlys Touya is a full-time employee of Lundbeck. Clément François was a full-time employee of Lundbeck at the time of the study initiation. Delphine Saragoussi and Patrice Verpillat were full-time employees of Lundbeck SAS at the time of the study. François-Xavier Lamy was a full-time employee of ICTA PM at the time of the study, a contract research organization under contract with Lundbeck. Adrian Tanasescu was a consultant for Rithme Consulting, a service provider consulting services working with pharmaceutical companies including Lundbeck at the time of the study and is currently an independent data science consultant. Bruno Falissard has been consultant for Lundbeck, E. Lilly, BMS, Servier, SANOFI, GSK, HRA, Roche, Boeringer Ingelheim, Bayer, Almirall, Allergan, Stallergene, Genzyme, Pierre Fabre, Astrazeneca, Novartis, Janssen, Astellas, Biotronik, Daiichi-Sankyo, Gilead, MSD, Lundbeck, Stallergene, Actelion, UCB, Otsuka, Grunenthal and ViiV. Christophe Lançon has been consultant for Lundbeck, Roche, and Janssen. Pierre-Michel Llorca has been consultant for Allergan, Janssen, Lundbeck, Otsuka, and Servier. Alan G. Wade received consultancy fees from Lundbeck.

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