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Development of a multimorbidity index: Impact on quality of life using a rheumatoid arthritis cohort

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ABSTRACT

Objective: To develop a multimorbidity index (MMI) based on health-related quality of life (HRQol).
Methods: The index was developed in an observational RA cohort. In all, 40 morbidities recommended as core were identified using ICD-9 codes. MMIs of two types were calculated: one by enumerating morbidities (MMI.count) and the other by weighting morbidities based on their association with HRQol as assessed by EQ-5D in multiple linear regression analysis (using β-coefficients; MMI.weight). MMIs were compared to the Charlson comorbidity index (CCI) and externally validated in an international RA cohort (COMORA Study).
Results: In all, 544 out of 876 patients were multimorbid. MMI.count was in the range 1–16 (median = 2) and MMI.weight in the range 0–38 (median = 1). Both indices were more strongly associated with EQ-5D than CCI (Spearman: MMI.count = −0.20, MMI.weight = −0.26, and CCI = −0.10; $p < 0.01$). R^2 obtained by linear regression using EQ-5D as a dependent variable and various indices as independent variables, adjusted for age and gender, was the highest for MMI (R^2: MMI.count = 0.05, MMI.weight = 0.11, and CCI = 0.02). When accounting for clinical disease activity index (CDAI) R^2 increased: MMI.count = 0.18, MMI.weight = 0.22, and CCI = 0.17, still showing higher values of MMI compared with CCI. External validation in different RA cohorts (COMORA, $n = 3864$) showed good performance of both indices (linear regression including age, gender, and disease activity $R^2 = 0.30$ for both MMIs).
Conclusion: In our cohort, MMI based on EQ-5D performed better than did CCI. Findings were reproducible in another large RA cohort. Not much improvement was gained by weighting; therefore a simple counted index could be useful to control for the effect of multimorbidity on patient's overall well-being.

1. Introduction

In the past decade, clinical and scientific interests in comorbidity and multimorbidity have increased [1–4]. However, the concepts of comorbidity and multimorbidity are used interchangeably [5]. Both concepts refer to being afflicted by more than one disease at the same time, but approach the patient from different perspectives [6]. As inflammatory rheumatic conditions are systemic diseases, a high prevalence of coexisting conditions can be observed. The average rheumatoid arthritis (RA) patient has 1.6 additional conditions, increasing with age, disease duration,

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Table 1
List of 40 chronic conditions: prevalence at baseline, beta-coefficients, and *p* values by linear regression analyses reflecting the association of each morbid condition with EQ-5D; assigned weights in accordance to beta-coefficients

Morbid condition	Prevalence, *n* (%)	beta-coefficient	*p* Value	Assigned weight
Glaucoma	4 (0.5)	0.129	0.076	0.5
Irritable bowel syndrome	9 (1.0)	0.082	0.051	0.5
Schizophrenia, bipolar disorder	7 (0.8)	0.075	0.058	0.5
Learning disability	7 (0.8)	0.067	0.059	0.5
Anorexia/bulimia	5 (0.6)	0.053	0.070	0.5
Migraine	13 (1.5)	0.053	0.043	0.5
Prostate disorders	36 (4.1)	0.040	0.026	0.5
Diverticulitis	22 (2.5	0.028	0.033	0.5
Chronic sinusitis	22 (2.5)	0.026	0.031	0.5
Hypertension	208 (23.7)	0.014	0.014	0.5
Cancer	114 (13.0)	0.010	0.016	0.5
Diabetes	65 (7.4)	0.006	0.020	0.5
Atrial fibrillation	27 (3.1)	0.002	0.033	0.5
Constipation	17 (1.9)	0.000	0.037	0.5
Multiple sclerosis	5 (0.6)	−0.001	0.067	1
Substance misuse	2 (0.2)	−0.001	0.105	1
Osteoporosis	109 (12.4)	−0.001	0.015	1
Psoriasis eczema	27 (3.1)	−0.003	0.028	1
Coronary heart disease	85 (9.7)	−0.004	0.021	1
Hearing loss	25 (2.9)	−0.010	0.030	1
Stroke/transient ischemic attack (TIA)	21 (2.4)	−0.015	0.036	2
Peripheral vessel disease	24 (2.7)	−0.021	0.034	2
Chronic kidney disease	25 (2.9)	−0.024	0.031	2
Inflammatory bowel disease	14 (1.6)	−0.025	0.043	3
Thyroid disorders	95 (10.8)	−0.025	0.017	3
Asthma	45 (5.1)	−0.030	0.024	3
Obesity	208 (23.7)	−0.042	0.012	4
Chronic liver disease	14 (1.6)	−0.050	0.039	5
Heart failure	28 (3.2)	−0.053	0.034	5
Bronchiectasis	9 (1.0)	−0.054	0.049	5
Depression	41 (4.7)	−0.064	0.027	6
Anxiety/neurotic disorders	32 (3.7)	−0.084	0.030	8
Alcohol problems	3 (0.3)	−0.087	0.091	9
Blind or low vision	7 (0.8)	−0.101	0.060	10
Parkinson	3 (0.3)	−0.104	0.086	10
Dyspepsia	22 (2.6)	−0.127	0.035	10
Chronic obstructive pulmonary disease (COPD)	0	−0.142[a]	0.072[a]	10[a]
Hepatitis (viral)	4 (0.5)	−0.142	0.072	10
Epilepsy	2 (0.2)	−0.205	0.113	20
Dementia	8 (0.9)	−0.211	0.053	20

[a] No COPD cases at baseline, beta-coefficient gained from multiple linear regression analyses including EQ-5D and COPD at year 1.

and/or disease activity [7–9]. Compared with the concept of comorbidity, where the index disease is at the center of interest, multimorbidity constitutes a more holistic, patient-centered concept [6].

To date, no gold standard exists on how to measure multimorbidity. A systematic literature review on assessing comorbidity and multimorbidity identified 39 different indices showing heterogeneity in terms of types and numbers of conditions included and outcomes the indices are based on. One of the most common indices used is the Charlson Comorbidity index (CCI) [10], which was originally developed as a prognostic index to predict 1-year mortality in a breast-cancer patient cohort. Research using a morbidity index based on mortality but studying outcomes different from death therefore might have misleading findings [11].

In chronic diseases, like RA, health-related quality of life (HRQoL) is the main outcome, associated with physical function, pain, and global health. It reflects patients' overall well-being, incorporating a multidimensional patient-centered concept. In a previous work we showed that an increasing number of morbidities leads to a decrease of HRQoL [12]. As rheumatology patients are typically afflicted by more than one disease, considering multimorbidity is of special importance when deciding on diagnostic or therapeutic strategies. Multimorbidity can cause polypharmacy, and an increasing treatment burden, which might also impact patients' overall HRQoL. Therefore, an index reflecting multimorbidity that is based on HRQoL might be helpful to better address the disease-related aspects of patients' overall well-being. This could also be useful for application in both clinical trials and epidemiological studies.

The purpose of this work was to create a multimorbidity index (MMI) based on HRQoL. We developed the MMI in RA patients, reflecting a typical cohort with a chronic condition. In further studies the new developed index should be validated in patients with different chronic rheumatic diseases and other conditions.

2. Material and methods

2.1. Study cohort

Patients were selected from the Brigham and Women's Rheumatoid Arthritis Sequential Study (BRASS), a prospective observational RA cohort including more than 1300 RA patients with longitudinal follow-up [13]. In BRASS, patients are included at any time point within their disease course, irrespective of disease duration or treatment initiation. Information about demographics and RA disease activity [including clinical disease activity index (CDAI), fatigue, functional status (Multidimensional Health Assessment Questionnaire, MDHAQ), and health-related quality of life (Euro-QoL 5 dimensions, EQ-5D)] is collected annually. For our

Table 2
Baseline characteristics of BRASS (development cohort) and the COMORA (validation cohort)

Baseline characteristics: mean (SD) or %	Development cohort, BRASS (n = 876)	Validation cohort, COMORA (n = 3864)
Age (years)	57.5 (13.5)	56.2 (13.0)
Female (%)	82.20%	81.8%
Disease duration (years)	13.2 (12.0)	9.6 (8.7)
White (%)	95.70%	NA
Never smoked (%)	52%	63.5%
Married (%)	65.30%	69.7%
1987 ACR criteria (%)	96.60%	91.3%
2010 ACR/EULAR criteria (%)	75.60%	88.1%
Rheumatoid factor (RF) positive (%)	64.20%	81.4%
Anti-CCP (ACPA) positive (%)	63.40%	NA
Tender joint count (28)	6.1 (7.5)	4.0 (5.4)
Swollen joint count (28)	5.0 (6.4)	2.7 (4.0)
Clinical disease activity index (CDAI)	16.8 (15.6)	13.7 (11.7)
C-reactive protein (mg/l)	7.5 (18.1)	NA
Erythrocyte sedimentation rate (mm/1 h)	NA	26.8 (22.7)
Euro-Qol 5 dimensions (EQ-5D)	0.81 (0.15)[a]	0.68 (0.28)[b]
Multidimensional Health Assessment Questionnaire (MDHAQ)	0.56 (0.5)	NA
Modified Health Assessment Questionnaire (MHAQ)	0.36 (0.4)	0.51 (0.57)
Current use of any DMARDs (%)	90.50%	93.5%
Current use of biological DMARDS (%)	45.40%	32.6%
Current use of NSAIDs (%)	50.50%	51.4%
Current use of steroids (%)	25.20%	54.5%
Counted multimorbidity index (median; IQR)	2 (1/3)	2 (1/3)
Weighted multimorbidity index (median; IQR)	1 (0/4.5)	0 (0/5.9)

[a] EQ-5D ranging from −0.109 to 1 [16,20].
[b] EQ-5D Index ranging from −0.59 to 1 [21].

study, baseline visit was defined as the first collection of EQ-5D. Out of 1049 patients, we included 876 patients with complete data on EQ-5D on two consecutive visits. All patients included in BRASS gave their written informed consent and the study was approved by the local Institutional Review Board.

2.2. Index development

2.2.1. STEP 1: Item generation: identifying morbid conditions

Multimorbidity was defined as "co-existence of two or more chronic diseases in one individual" [14]. We selected morbid conditions in accordance to a large cross-sectional study recently published [1], using more than 1 million patients: morbidities were identified by a systematic literature review [2] and defined as chronic (long-term) disorders with important impact by the National Health Service of Scotland. A listing of the 40 chronic conditions including their prevalence in the study cohort is shown in Table 1. BRASS patients were linked to the Research Patient Data Registry (RPDR), a centralized clinical data registry, including over 1 billion records from patient encounters, laboratories, and other medical care from hospitals or providers within the Partners HealthCare System [15]. Selected morbidities identified by International Classification of Diagnosis, Ninth Revision (ICD-9), codes were assigned to a given BRASS visit if reported in RPDR at least once within 1 year prior to and after the BRASS visit.

2.2.2. STEP 2: Development of the multimorbidity index (MMI)

As we intended to create an MMI based on HRQoL, we used EQ-5D as the outcome of interest. EQ-5D is a five-dimensional health state classification based on patients' preferences on a 0−1 scale, where 1 represents perfect health and 0 represents death [16]. Values of EQ-5D at baseline were used as the dependent variable in linear regression analyses.

Two different MMIs were developed: a simple count of morbid conditions per patient at baseline (MMI.count) and a weighted count (MMI.weight) based on HRQol. Weights were derived by entering all 40 morbid conditions as binary (1 = present, 0 = absent) independent variables in multiple linear regression analyses, using EQ-5D as the dependent variable, to calculate β-coefficients. To preclude multicollinearity we calculated variance inflation factors which were less than 2. Different conditions were weighted according to their β-coefficients, which reflect the association of a given morbid condition and HRQoL. To facilitate calculations of the weighted index, β-coefficients were transformed as follows: $>0 = 0.5$; 0 to $-0.014 = 1$; -0.015 to $-0.024 = 2$; -0.025 to $-0.034 = 3$; -0.035 to $-0.044 = 4$; -0.045 to $-0.054 = 5$; -0.055 to $-0.064 = 6$; -0.065 to $-0.074 = 7$; -0.075 to $-0.084 = 8$; -0.085 to $-0.094 = 9$; -0.095 to $-0.15 = 10$; less than $-0.2 = 20$. The β-coefficients as well as the transformed weights are depicted in Table 1.

2.2.3. STEP 3: Internal validation and comparative assessment of the MMI

To compare the performance of the new MMIs with an existing, valid index we calculated the Deyo-adapted Charlson comorbidity index (CCI) [17] and used it as the primary comparator, as well as the functional comorbidity index (FCI) [18] in the same population used for development of MMI. We performed linear regression analyses, using EQ-5D as the dependent variable and either the CCI, FCI, or the new MMIs as independent variables. Models were adjusted for age, gender, and RA disease activity. We calculated 95% confidence interval for R^2 values as well as their differences by bootstrapping. We generated 1000 samples, and used the percentile method to produce 95% confidence intervals. The R^2 difference was considered statistically significant when the 95% confidence interval of the difference did not include the null value of zero. We also tested several aspects of validity. (A) *Content validity* refers to the extent to which a measure covers all facets of a given construct. (B) *Criterion validity* is the extent to which the new index correlates with an existing one with the same construct: we therefore correlated the MMIs with CCI and FCI as well as HRQol, all measured at the baseline visit, using Spearman's correlation. Using linear regression we calculated predictive values of EQ-5D using MMI, age, and gender as independent variables and EQ-5D at year 1 as a dependent variable. Predicted versus observed values of EQ-5D were correlated and differences depicted by a

Table 3
Relationship of various indices with health-related quality of life (HrQol) function and fatigue

Index	Explained variability of EQ-5D[a]			Spearman correlation[b]				
	R^2 crude model	R^2 adjusted model (incl. age, sex)	R^2 adjusted model (incl. age, sex, and CDAI)	CCI	FCI	EQ-5D	MDHAQ	Fatigue
Counted multimorbidity index (MMI.count)	0.05*	0.05*	0.18*	0.16	0.81	−0.20	0.28	0.20
Weighted multimorbidity index (MMI.weight)	0.10*	0.11*	0.22*	0.18	0.87	−0.26	0.34	0.25
Weighted multimorbidity index using beta-coefficients	0.13*	0.14*	0.24*	0.15	0.68	−0.28	0.30	0.24
Charlson comorbidity index (CCI)	0.01*	0.02*	0.17*	1	0.20	−0.10	0.17	0.12
Functional comorbidity index (FCI)	0.06*	0.07*	0.18*	0.20	1	−0.21	0.32	0.23

CCI, Charlson Comorbidity Index; CDAI, clinical disease activity index; FCI, Functional Comorbidity Index; EQ-5D, Euro-quality of life 5 dimensions; incl, including; MDHAQ, Multidimensional Health Assessment Questionnaire.

* $p < 0.001$.

[a] R^2 obtained by linear regression models using EQ-5D as a dependent variable and various indices as independent variables (2nd column); models are adjusted for age, sex (3rd column), and CDAI (4th column); weighted multimorbidity index (MMI.weight) showed the highest R^2.

[b] Spearman correlation of the multimorbidity indices with existing comorbidity indices, HRQoL (EQ-5D), function (MDHAQ), and fatigue.

Bland–Altman plot (plotting mean difference between observed and predicted against the mean of observed and predicted values). (C) *Predictive validity* refers to the degree the new index predicts HRQoL measured in the future. We therefore correlated MMI with EQ-5D year 1, calculated predictive values of EQ-5D at year 1 using linear regression, and compared predicted versus observed values.

2.2.4. STEP 4: External validation

External validity of MMIs was tested in RA patients included in the COMORA study. COMORA is an international, cross-sectional, observational study of more than 4500 RA patients recruited in 17 countries worldwide [19]. Specific morbidities (see Supplement Table S1) were collected during an interview, along with variables of disease activity and severity. We calculated the counted and weighted MMI and investigated its relationship with EQ-5D using Spearman correlation and linear regression analyses (as described above). Predicted versus observed values of EQ-5D were correlated and differences depicted by a Bland–Altman plot.

3. Results

Baseline characteristics of 876 RA patients are depicted in Table 2, showing a typical RA clinical cohort. In total, 544 patients (62.1%) were considered as multimorbid, having at least one chronic condition in addition to RA. The mean number (SD) of morbid conditions was 2.62 (2.1). The highest prevalence was found for hypertension (23.7%), obesity (23.7%), cancer (13.0%), and osteoporosis (12.4%) (Table 1).

3.1. Development of MMI

The unweighted, counted index (MMI.count) at baseline was in the range 1–16 (median = 2; IQR = 1/3). By transforming β-coefficients from multiple linear regression analyses into weights (as described above), we created a weighted multimorbidity index (MMI.weight) based on HRQoL. At baseline, MMI.weight was in the range 0–38 (median = 1; IQR = 0/4.5).

3.2. Internal validity and comparative assessment of the MMI

In linear regression models using EQ-5D as the dependent variable and MMIs, CCI, or FCI as independent variables, R^2 was the highest for MMI.weight ($R^2 = 0.10$), compared with FCI ($R^2 = 0.06$), MMI.count ($R^2 = 0.05$), and CCI ($R^2 = 0.01$) ($p < 0.001$ for all models; 2nd column of Table 3). When we included age and gender in the models, R^2 increased slightly (3rd column Table 3). After including CDAI in our regression models to account for RA disease activity, we still found significant association of MMI with EQ-5D and an increase of the R^2 (4th column of Table 3). Disease duration was not statistically significant; therefore it was not included in the models. Using bootstrapping, we could confirm better performance of the models including MMIs with significant differences of R^2 between MMI.count and CCI, and between MMI.weight, CCI, and FCI (Supplement Table S2).

We included 40 different chronic morbid conditions covering all body systems, demonstrating the *content validity* of MMI. The morbidities included were selected according to a literature review and discussed by several authors (H.R., K.Y., M.D.M., and D.H.S.), all clinical and experienced research rheumatologists.

Criterion validity was tested using Spearman correlation, which showed low but significant correlation of both MMI with CCI (MMI.count, $r = 0.16$; MMI.weight, $r = 0.18$; $p < 0.001$) and high correlation with FCI (MMI.count, $r = 0.81$; MMI.weight, $r = 0.87$; $p < 0.001$). Correlation with EQ-5D was moderate for all four indices, showing the highest correlation of MMI.weight ($r = -0.26$, $p < 0.001$) (Table 3). We also found moderate but significant correlation of both MMI with physical function and fatigue, again showing the highest correlation of MMI.weight ($r = 0.34$ for MDHAQ; $r = 0.25$ for fatigue; $p < 0.001$; Table 3). The relationship between both MMIs and EQ-5D is shown in Fig. 1, depicting a decrease of EQ-5D with increasing MMI, following a linear trend. Correlation of predicted and observed values of EQ-5D at baseline was 0.22 for MMI.count and 0.28 for MMI.weight ($p < 0.01$ for both). Bland–Altman plots in general showed good concordance, but less agreement and higher values of predicted EQ-5D in patients with lower quality of life (left lower corner of the plot; Fig. 2). This overestimation was mainly observed in patients with higher disease activity (Fig. 2).

To test *predictive validity* we correlated the MMI at baseline with EQ-5D at year 1: MMI.count, $r = -0.30$, MMI.weight, $r = -0.35$ ($p < 0.001$ each). Correlations of predicted and observed values of EQ-5D at year one calculated by regression analysis were almost similar for both MMIs: MMI.count, $r = 0.34$; MMI.weight, $r = 0.37$ ($p < 0.001$ for both models).

3.3. External validation of MMI

In COMORA, 3864 RA patients with complete data on EQ-5D were available and included for external validation. Baseline characteristics are depicted in Table 2 (last column). In total, 2528 patients (65.4%) were identified as multimorbid; morbidity conditions as well as their prevalence are reported as supplementary files (Supplement Table S1). Median MMI.count was 2 [interquartile

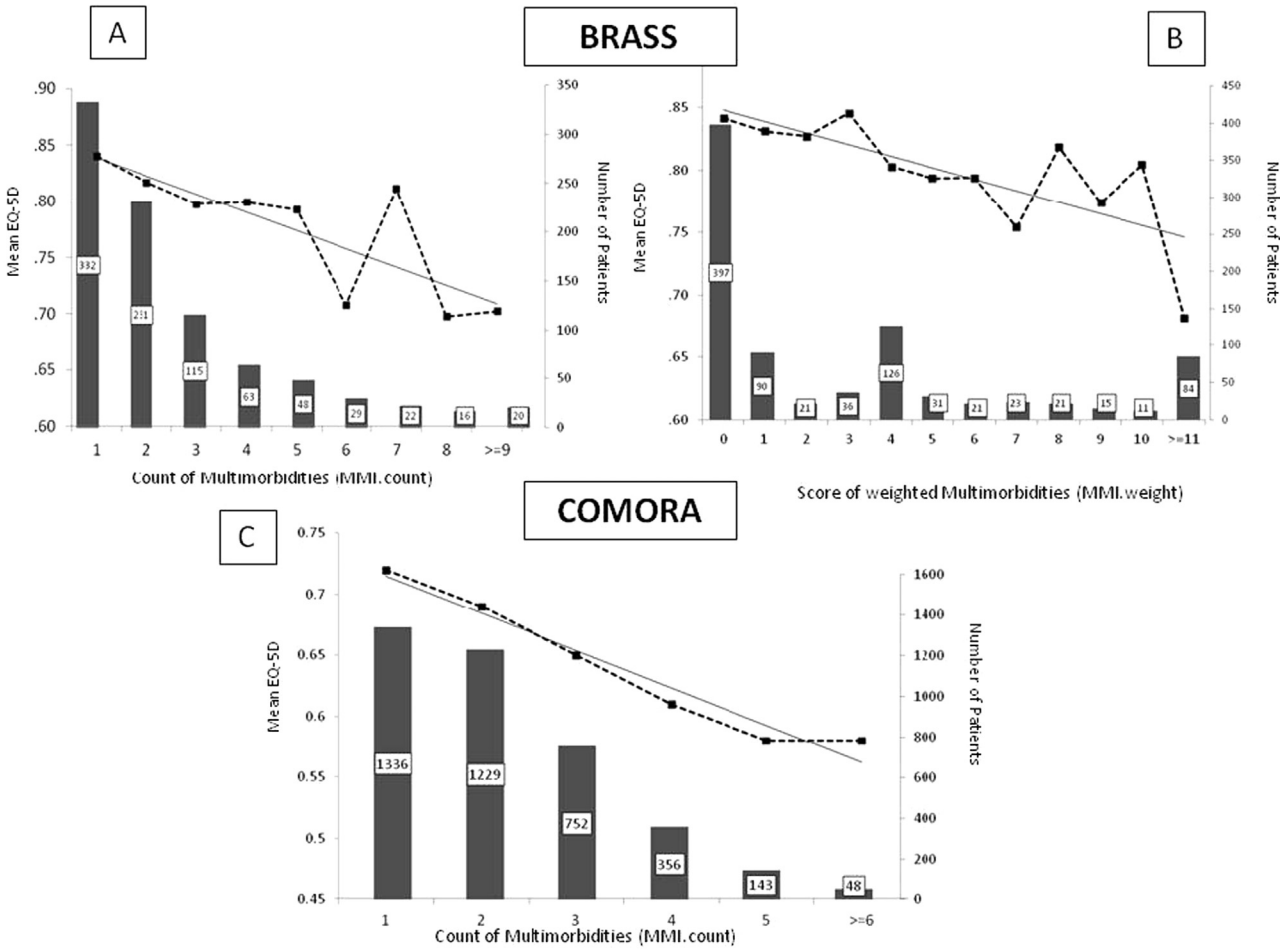

Fig. 1. Relationship of multimorbidity indices (counted multimorbidity index, MMI.count; weighted multimorbidity index, MMI.weight) with health-related quality of life (EQ-5D) in BRASS cohort (A and B) as well as in the validation cohort (COMORA, C) follows a linear trend. The histogram indicates the number of patients with respective MMI, the dotted line the mean EQ-5D, and the solid line the smoothed linear trend line of mean EQ-5D.

range (IQR), 1/3] and median MMI.weight was 0.5 (IQR, 0/5.8). EQ-5D correlation was low, but significant, with MMI.count ($r = -0.15$; $p < 0.01$) and MMI.weight ($r = -0.13$; $p < 0.01$). EQ-5D decreased with increasing value of MMI.count following a linear trend (Fig. 1C). The variance of EQ-5D explained by MMIs was the same for MMI.count and MMI.weight ($R^2 = 0.03$ for both); when we included disease activity (CDAI) in the model R^2 increased ($R^2 = 0.32$ for both MMI.count and MMI.weight). Correlation of predicted and observed values of EQ-5D was significant for both indices ($r = 0.18$ for MMI.count; 0.17 for MMI.weight; $p < 0.01$ for both), plotted in the Bland – Altman Plots (Fig. 2C and D).

4. Discussion

We developed and validated an index that unifies two important multidimensional concepts—multimorbidity and HRQoL. This MMI is novel, as existing indices are commonly comorbidity indices based on more specific outcomes, such as mortality, costs, or function, and therefore may not address a patient's overall condition [2,10,18]. The MMI is the first index that systematically includes chronic conditions and may be useful across rheumatic diseases. Both MMIs (counted and weighted) can be used in clinical research to control for the effect of multimorbidity on patients' overall well-being and may be useful for clinical practice.

We decided to base our indices on HRQoL, as it is a holistic concept referring to the physical, emotional, and social impact of disease and related treatments. Instruments to measure HRQoL, such as the EQ-5D, are not specific to any age, disease, or treatment and could be used across many populations and different conditions. Multimorbidity embraces a holistic clinical approach, assessing a patient with more than one morbidity from a different perspective. In contrast with the concept of comorbidity, it puts the patient rather than a single condition as the focus of interest [6]. The MMIs presented in our study allow one to account for the impact of "being afflicted by more than one disease" on the patients' overall well-being. The criteria for selecting diseases included in existing multimorbidity and comorbidity indices vary. In a systematic literature review on common morbidity indices, the authors found that the majority of studies do not explain the selection procedure. Often, the list of diseases included is based on pragmatic reasons, such as availability of data or prevalence of disease [2]. For the MMI, diseases were selected as either recommended as a core for any multimorbidity measure by a systematic literature review and/or defined as "chronic (long-term) disorders with important impact" as proposed by the National Health Service Scotland [1,2]. These selection criteria make the MMI more robust and versatile in different cohorts. Another strength of our study is the collection of morbidity conditions, as we had access to a centralized clinical data registry, which ensures accurate assessment and report of morbidities. As shown previously, the positive predictive value (PPV) of claim-reported diagnoses ranges from 44.8% to 96.3% depending on the disease of interest and the algorithm used [22–24]. We included conditions reported at least once in RPDR within the period of interest, which might decrease specificity and lead to an

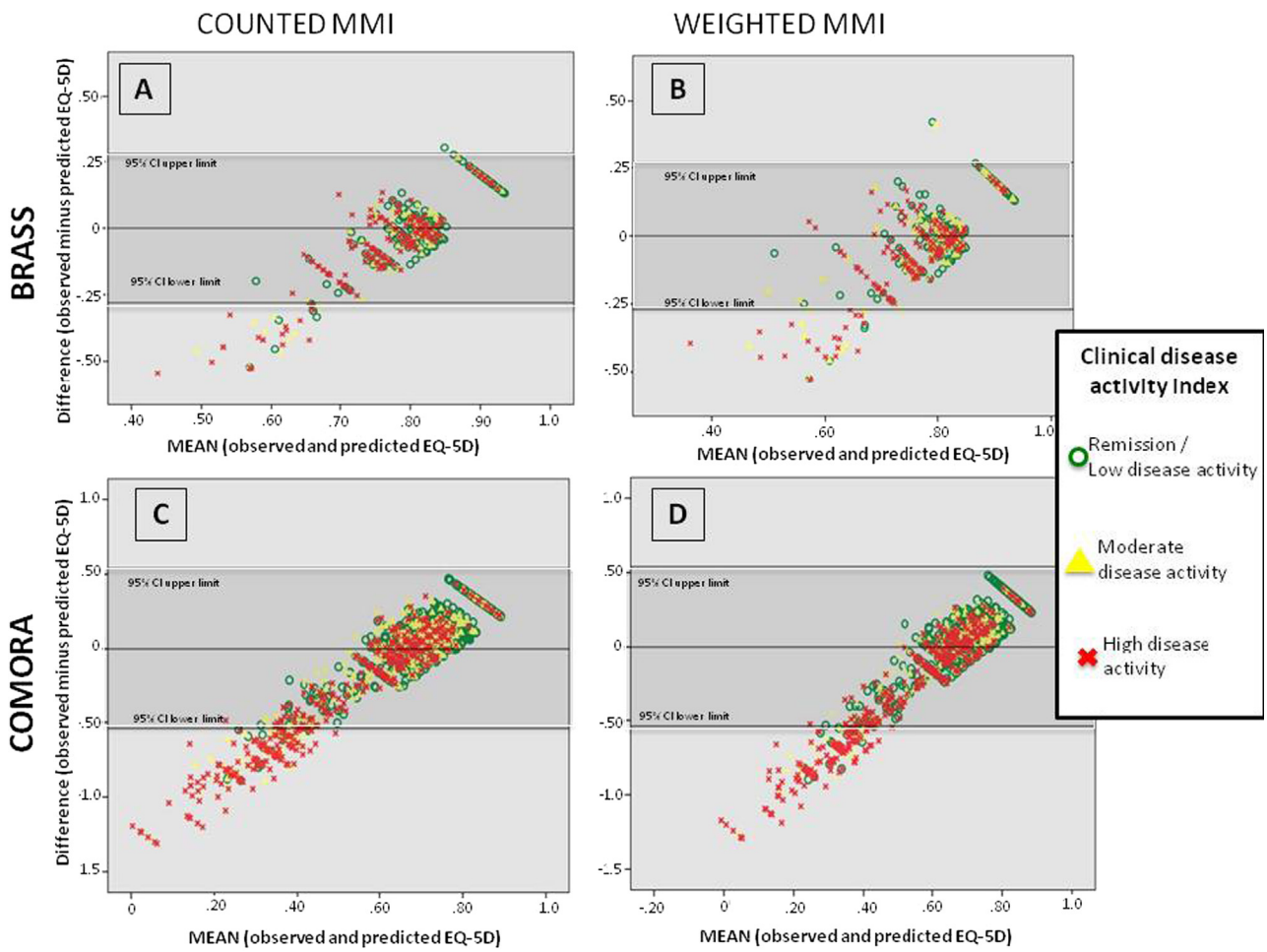

Fig. 2. Bland–Altman Plot visualizing agreement between predicted and observed mean values of Euro-Qol 5D, calculated by linear regression models including age and gender and multimorbidity indices as independent variables: BRASS [development cohort; upper row: count of multimorbidities (MMI.count) (A) and weighted multimorbidity index (MMI.weight) (B)] and COMORA [validation cohort; MMI.count (C); and MMI.weight (D)]. High accordance of predicted and observed value is grouped around zero and 95% limit of agreement marked by the upper and lower line (highlighted in gray). Values below zero indicate higher predicted EQ-5D than observed EQ-5D. This could mainly be found for patients with lower EQ-5D and higher states of disease activity (yellow and red labels in the left lower corner of all panels). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

overestimation of prevalence of certain condition. However, looking at prevalence rates in the study cohort, we could find no systematic overestimation, showing similar prevalence rates for many conditions as reported in published literature [25–29].

We compared our MMIs to two existing and commonly used tools: the Charlson comorbidity index (CCI) and the functional comorbidity index (FCI). MMI.weight showed the highest correlation with HRQol, physical function, and fatigue compared with other indices. Furthermore, MMI.weight explained more of the variance of EQ-5D than any other index. In comparison, the MMI.count showed lower correlation and variance explained compared with FCI, but still better performance than did the commonly used CCI. We also showed that both indices are able to predict HRQoL after 1 year. MMI.count offers a good alternative to MMI.weight, which might be regarded as complicated and less feasible due to the different weights and large number of morbidities included. Thus, MMI.count might be more appropriate for studies with limited data on morbidities or everyday use whereas more sophisticated epidemiological studies might benefit from the more precise MMI.weight.

We also validated our indices in a different, large cohort of more than 3800 RA patients. We were able to replicate the agreement of HRQoL with MMIs and found a linear relationship between MMI.count and EQ-5D (Fig. 1C), fully supporting the data obtained in the BRASS derivation cohort.

Several limitations need to be addressed: first, the development of the indices was performed in a single-center RA cohort, rather than in the general population. Findings may not be generalizable, and we do not have a comparison to a non-RA population. Nevertheless, we had a large cohort of almost 900 RA cases with longitudinal follow-up and validated our findings in an even larger, international cohort. This is a strength of the study when compared with existing indices, which were developed in smaller cohorts or with cross-sectional data only [10,18]. Even though the development was performed in a disease-specific cohort, RA was not regarded as an index disease as it would be for a comorbidity index. To calculate MMI.count we treated RA as any other condition in a multimorbid patient, assigning one point per condition.

Second, we did not consider severity in our index. This is mainly due to pragmatic reasons to provide better feasibility. Severity ratings would provide more accurate adjustment, but as documentation of disease symptoms and severity varies greatly, this would lead to poor reliability. As we did not account for severity of any morbidity included, we also did not account for RA disease activity in the development model. When we did include CDAI we derived only slightly different weights and no better overall performance of the weighted index (data not shown). In secondary regression models including MMI and CDAI, the explained variance for the EQ-5D increased, still showing

significant impact of multimorbidity. Overall, the variation of EQ-5D explained by using any index is low. Several factors known to be related to HRQoL, such as fatigue, pain, or socioeconomic status, were not included in the model. We never intended to create the best model explaining HRQoL; rather we used HRQoL to facilitate development of an index accounting for the impact of multimorbidity on the patient's well-being. We found that MMI performed significantly better than CCI or FCI.

In our study we tested predictive validity of MMIs, demonstrating good performance of predicting HRQoL. In further studies it would be interesting to explore if these indices also predict other outcomes such as mortality or health care utilization.

We used β-coefficients from linear regression models to create weightings for each morbid condition based on its relationship with HRQoL. Although some morbidities had a significance greater than 0.05, we included them in the index, as significance was mainly influenced by sample size and prevalence of morbid conditions. This might also be the explanation for some morbidities having a positive association with EQ-5D (β-coefficients > 0). We therefore did include them also, assigning the lowest weight of 0.5. Weights and their cut-offs were chosen somewhat arbitrarily, taking into account the range of derived β-coefficients. The transformation of beta-coefficients into integers was done for pragmatic reasons, to facilitate calculation of MMI.weight. A weighted index, strictly based on beta-coefficients, performed marginally better than the index based on simple points (Table 3). However, the integer scores are easier to use and more practical.

In the COMORA Study used for external validation, data on only certain morbidities were collected via interviews. Therefore we did not have information on all morbidities included for development of MMI. Nevertheless, in COMORA the most important and most prevalent morbidities of RA patients were collected [19]. Even though we were not able to get data on all morbidities included in the original MMI, the performance of both MMIs in COMORA was good. This not only provided additional validity to the MMI but also indicates that MMI may be a valuable tool even in cohorts of patients with incomplete morbidity datasets. Furthermore, this shorter version of the MMI might be a valid alternative, which needs to be further examined and validated in other cohorts.

5. Conclusion

In conclusion, both versions of the MMI are valid tools to adjust for multimorbidity and its effect on patients' overall well-being. This may be important for any treatment study when HRQoL is the outcome of interest as well as daily clinical routine when treating multimorbid RA patients. Both versions of the MMI outperformed the CCI, which is commonly used but not validated for outcomes such as HRQoL. Not much improvement was gained by weighting; therefore a simple counted index (MMI.count) appears to constitute a feasible instrument to control for the effect of multimorbidity on HRQoL. Further work is necessary to validate the new indices in non-RA patient populations.

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Appendix A. Supplementary Information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.semarthrit.2015.06.010.

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