**TITLE**

Older patients at risk of deterioration in health-related quality of life were accurately identified by a prognostic model developed and validated based on the PROPERmed individual participant data database.

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**ABSTRACT**

**Objective** - To develop and validate a prognostic model to predict deterioration in health-related quality of life (dHRQoL) in older general practice patients with at least one chronic condition and one chronic prescription.

**Study design and setting** -We used individual participant data from five cluster-randomized trials conducted in the Netherlands and Germany to predict dHRQoL, defined as a decrease in EQ-5D-3L index score of 5 % after six-month follow-up in logistic regression models with stratified intercepts to account for between-study heterogeneity. The model was validated internally, and by using internal-external cross-validation (IECV).

**Results** – In 3,582 patients with complete data, of whom 1,046 (29.2 %) showed deterioration in HRQoL, 12/87 variables were selected that were related to single (chronic) conditions, inappropriate medication, medication underuse, functional status, well-being and HRQoL. Bootstrap internal validation showed a C-statistic of 0.71 (0.69 to 0.72), and a calibration slope of 0.88 (0.78 to 0.98). In the IECV loop, the model provided a pooled C-statistic of 0.68 (0.65 to 0.70) and calibration-in-the-large of 0 (-0.13 to 0.13). HRQoL/functionality had the strongest prognostic value.

**Conclusion** – The model performed well in terms of discrimination, calibration, and generalizability and might help clinicians identify older patients at high-risk of dHRQoL.

**Registration** - PROSPERO ID: CRD42018088129

**Keywords** –

Multimorbidity, polypharmacy, elderly, patient-centred care, quality of life, functional status, prognostic model.

**Running title**

A prognostic model to predict deterioration in health-related quality of life in older patients with multimorbidity and polypharmacy.

**Word count**

3671

**WHAT IS NEW**

*Key findings*

The PROPERmed prognostic model of future deterioration in health-related quality of life in older patients with multiple conditions and medications performed well in discrimination, calibration, and showed promising generalizability.

The strongest predictors in the model were health-related quality of life and functional status at baseline.

*What does this add to what is already known?*

PROPERmed-dHRQoL is the first prognostic model to predict deterioration in health-related quality of life in older patients with multiple conditions and medications that is based on an individual participant data meta-analysis.

*What is the implication, what should change now?*

External validation studies should confirm generalizability beyond internal-external cross-validation.

Measures of health-related quality of life and functional status at baseline, which proved to be the two prognostic variables that are of outstanding relative importance in the prognostic model, might help physicians to detect patients with multimorbidity and polypharmacy at risk for a potentially preventable deterioration.

**INTRODUCTION**

In aging populations, the increased incidence and severity of multiple (chronic) conditions (two or more) leads to deterioration in health-related quality of life (dHRQoL) (1). Patients with multiple conditions usually have several drug prescriptions (five or more), which increases the risk of overuse, underuse and misuse of medications (2). Potential consequences, such as falls, cognitive decline, loss of autonomy, and hospital admissions, are often severe and may contribute to dHRQoL, a key patient-reported outcome and one of the most relevant in older life (3–5).

Complex drug regimens and high treatment burden make the management of multimorbidity a significant challenge for physicians (6). They are also expensive for health care systems worldwide because they lead to an increase of health care utilization and cost (7). However, not all patients with multiple morbidities need complex care (8). As the multimorbid population is heterogeneous, it would be helpful to identify patients at high risk of dHRQoL because those with high baseline risk and/or higher severity of disease may generally be expected to benefit more from (complex) interventions (9). Furthermore, risk stratification may help allocate resources to the high-risk patients that are expected to benefit most from targeted interventions (10–12).

Prognostic models are generally considered to be important tools to help target interventions and improve clinical and economic outcomes (13). When focusing on dHRQoL, it is of fundamental importance to hinder as far as possible the natural slow decline in longitudinal trajectories of HRQoL punctuated by episodes of serious exacerbations that lead to hospital admissions (14,15), or, in other words, to provide ‘upstream’ preventive care to patients in need before ‘downstream’ morbidity and expenditures occur (13). High-performance prognostic models may be used to detect patients in need of supportive care (e.g. geriatric assessment and medication review) (10–12,16).

To the best of our knowledge, no dHRQoL prognostic model for older patients with multiple chronic conditions and polypharmacy exists. We therefore aimed to develop and validate a model to predict dHRQoL after six months of follow-up in older patients with at least one chronic condition and one chronic prescription, based on an individual participant data meta-analysis (IPD-MA). We used the IPD from a previously harmonized database that contains comprehensive patient-related data on socio-demographics, morbidity, medication, functional status, and well-being from five recent cluster-randomized trials conducted in German and Dutch general practices. We chose a prognostic modelling approach based on IPD-MA because it offers both statistical and clinical advantages over other modelling techniques by permitting the assessment of generalizability. Furthermore, the increased sample size and case-mix variability it provides may reduce overfitting and thus improve external performance (17).

**MATERIALS AND METHODS**

**Source of data**

We harmonized individual participant data (IPD) from five cluster-randomized trials that were conducted in the Netherlands and Germany between 2009 and 2012 to optimize pharmacological treatment in older chronically ill patients **(Supplemental Table 1)**. Although conducted in different health care systems, the included trials, namely ISCOPE (18), Opti-Med (19,20), PIL (Nederlands Trial Register, NTR2154) (21), PRIMUM (8,22), and RIME (Deutsches Register Klinischer Studien-ID, DRKS00003610), resemble each other in terms of key study characteristics. Four trials (PRIMUM, Opti-med, PIL, and RIME) compared a structured medication review consisting of several intervention components (i.e., complex interventions) with usual care, while ISCOPE used a functional geriatric approach to compare usual care with a proactive and integrated care plan. Details of the origin and preparation of the source data for the PROPERmed database (PRIMUM, Opti-Med, PIL, ISCOPE, RIME) will be published elsewhere.

[About here link to: Supplemental Table 1 on Main characteristics of the included trials]

**Participants**

At baseline, we included general practice patients aged 60 years or older with at least one chronic condition and one chronic prescription. We defined chronic conditions in accordance with O´Halloran´s list (23), and chronic prescriptions in the same way as the included trials (two weeks duration in PRIMUM, two months in ISCOPE, and three months in Opti-Med, PIL and RIME).

**Outcome**

We defined dHRQoL as a decrease of at least five percent from baseline to six-month follow-up in the 5 dimensions 3 level version of EuroQoL (EQ-5D-3L), operationalized using a Likert score. We considered this cut-off as clinically relevant because it corresponds to several studies’ estimates of patients’ perceptions of minimal important difference (MID) (24–26). In two of the Dutch trials (ISCOPE and PIL), the question relating to the item “mobility” was slightly modified from the original instrument, as it was frequently a missing value in older Dutch populations due to misinterpretation (27).

**Prognostic variables**

For candidates at baseline, 87 prognostic variables relating to socio-demographics, lifestyle, morbidity, medication, functional status, and well-being were considered for inclusion in the modelling process. The allocation of patients to control and intervention groups was also considered.

*Socio-demographics and lifestyle*

We collected IPD on age, sex, living situation, and educational level (28) from the trials. Information on smoking status was provided in three (PRIMUM, PIL, and RIME) of the five trials.

*Morbidity*

We used the second version of the International Classification of Primary Care (ICPC-2) (29) to describe a common list of individual chronic conditions across trials (patient-reported in RIME; in all others we used physician-reported information) and used a modified version of the Diederichs list for morbidity count, which included 15 of the 17 conditions identified in a systematic review (i.e. dementia, kidney and peripheral artery disease were not provided in two of the five trials) (30). The Charlson comorbidity index (31) was provided in two of the trials (PRIMUM and RIME), but could not be calculated for the other trials (e.g. because no information was provided on condition severity).

*Medication*

Potentially inappropriate prescriptions and medication underuse were mainly assessed using patient-reported medication data (except from ISCOPE which provided physician-reported information) by applying the criteria used in the EU-PIM list (32), STOPP-START criteria (33), the high-risk prescribing criteria applied by Dreischulte et al. (34), the Anticholinergic Drug Scale (ADS) (35,36), the Drug Burden Index (DBI) as a count variable (as the dosage that would have allowed the calculation of the index score was not available in the majority of IPD (37–39)), and Anticholinergic Drug Burden (ADB) (40).

*Functional status and well-being*

Trials used various instruments to measure functional status such as the Katz-15 (combination of KATZ-6 and Lawton IADL) questionnaire (41), the 13-item vulnerable elderly survey (VES-13) (42), and the Geriatric Giants VAS (GGV) scale (0-10) (43) developed *ad hoc* by one of the trials (Opti-Med). To standardize the metrics used in the scales of the instruments employed in the different trials, numerical values were subtracted from their overall mean (i.e., centred) and subsequently divided by their standard deviations (i.e., scaled) to obtain comparable values that would, however, require back-transformation for clinical interpretability.

The trials assessed the presence of depressive symptoms using different questionnaires (the 15-item Geriatric Depression Scale (GDS) (44,45), GDS-5 (46), SF-12 (47,48), and SF-36 (49). We considered the standardized mean differences of the various instruments for the modelling approach. The presence of depressive symptoms was used as a binary variable for descriptive purposes and derived from the cut-offs of the original questionnaires used in the various trials.

The presence of pain was defined as a binary variable using the categorical classification (no pain or any pain regardless of intensity) from the von Korff index (50), the SF-12 (47,48), the SF-36 (49), and the self-developed VAS scales or single questions used in two of the trials (i.e. Opti-Med, ISCOPE).

Regarding HRQoL at baseline, we used the above described EQ-5D-3L index score (51). In addition, we considered the two independent subscales from the HRQoL Comorbidity Index (52–54) as prognostic variables **(Supplemental Table 2)**.

[About here link to: Supplemental Table 2 on Prognostic variables and their definitions]

**Sample size**

The sample size reflected the number of available observations in the included trials. In order to calculate achievable performance based on the available sample size, we applied the formulae for minimum sample sizes (55). As we applied the calculation retrospectively, the sample size calculation only has exploratory character. This was part of the process of developing multivariable prediction models to obtain estimates for the heuristic shrinkage factor caused by the number of candidate predictors (55). Based on the sample size of our complete-case analysis and the use of empirical estimates of C-statistics and event frequencies to approximate the prediction model Cox-Snell R-squared’s apparent performance (Cox-Snell *R2* of 0.12), we would expect a heuristic shrinkage factor of 0.84 which we considered acceptable.

**Missing data**

In addition to the core analysis of complete cases, we conducted sensitivity analyses using the missing-indicator method (MIM) (56,57) and multiple imputation. For the latter, we conducted six multiple imputations (MI) in five iterations (58), and pooled them according to Rubin’s Rules (59). For the original trials, stratification was used to graphically explore missing data patterns (60,61). This revealed the various contributions of sporadically and systematically missing values (variable not recorded in the trials). We performed multi-level multiple imputation to adjust for within-trial and between-trial variability (62).

When values were missing systematically, we did not consider the associated candidate prognostic variables in any of the trials (i.e. smoking status, Charlson comorbidity index).

**Statistical analysis methods**

*Modelling framework to deal with within-study correlations and between-study heterogeneity in the IPD*

Prognostic model development and validation relied on an established framework for developing and evaluating clinical prediction models in an IPD-MA (17). By virtue of their origins in different independent trials, the clustered data structure first had to be addressed. A stratified intercept model was fitted, which provided a different baseline risk for each trial. This approach was selected over a random intercept model because the validity of the normality assumption for the random intercept in differing random effects models cannot be checked and is open to doubt when five trials are conducted in different health care systems. A generalized linear model was therefore chosen using the logit link function (i.e., logistic model). To improve interpretability, we used effect coding rather than dummy coding in order to estimate trial-specific baseline risks (63). This produces a global intercept (overall average) and shows the deviation from the average for each trial. While in a one-stage meta-analysis for model development and internal validation, the study indicators account for the origin of the data, each study serves as a validation sample in an applied internal-external cross validation (IECV) (17,64).

*Model development and variable selection*

When developing the model, we defined it structurally by selecting variables using the so-called *Least Absolute Shrinkage and Selection Operator* (LASSO) (65). Age (assumed, like the other continuous variables, to be linearly associated with outcome), sex, and the effect-coded indicators reflecting the trials’ baseline risk, were not regularized. In order to obtain sparser models, we moved away from the default setting, which would have meant choosing the tuning parameter lambda as the value with the minimum mean cross-validated error (“optimal penalty”). In preference, we decided to be stricter and chose the most regularized model, meaning that the error was within one standard error of the minimum (“1-se rule” (66)). Variable importance was derived from the ranks of the absolute values of the final (standardized) coefficients (65). For subsequent cases, the model formula obtained using the LASSO technique was applied to models that were refitted using unpenalized maximum likelihood. We additionally calculated a uniform shrinkage factor from bootstrap internal validation; the uniform shrinkage factor corresponds to one minus the average of all calibration slopes of each bootstrap model applied to the original IPD.

*Performance metrics*

Predictive performance was assessed by simultaneously using 250 bootstrap samples internally (67), and employing IECV to assess generalizability (17,64). Model performance in terms of discriminatory ability to differentiate patients with dHRQoL from the rest was quantified using the C-statistic (equivalent to the area under the receiver-operating characteristic curve, ROC). Performance metrics for model calibration to assess agreement between observed event frequencies and predicted probabilities were based on the slope of the calibration curve and calibration-in-the-large (CITL), and additionally inspected visually by means of calibration plots (68).

*Model validation*

With regard to internal bootstrap validation, the prediction model was developed *de-novo* for each of the 250 bootstrap samples, thus maintaining the proportions of the original trial data in the IPD. Performance metrics were calculated from models fitted to the bootstrap samples that were subsequently applied to the original IPD. The mean difference across all bootstrap samples was the estimated optimism, while the optimism-corrected performance metric was obtained by subtracting estimated optimism from the original apparent performance metric.

In IECV loops in particular, CITL was used to reflect overall calibration. Mimicking the application in a new population, the IECV loop repeatedly selects variables and thus fits a prediction model in all but one of the IPD trials (i.e. training set), while also checking predictive performance in the omitted study (i.e. test set). We chose the conservative option of the average intercept of the IECV training set. As they are of special importance for external validation, we extracted the C-statistic and CITL estimate for each omitted study at each stage of the IECV loop (69). Based on the within-study correlation between the C-statistic and CITL obtained using a non-parametric bootstrap (70), the respective estimates were pooled using multivariate random-effects meta-analysis (71). Taking a Bayesian approach with an uninformative prior distribution, a multivariate *t*-distribution (of the pooled means and covariance matrix from the multivariate meta-analysis) was used as an approximate posterior distribution to assess the model’s combined discrimination and average calibration performance. Requiring at least modest discriminatory ability of 0.65 and a CITL between -0.1 and 0.1, the proportion of samples from the posterior distributions that achieved this allowed us to calculate the probability of satisfying these requirements (70).

*Technical implementation and reporting*

All analyses were conducted using the R software environment in version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) with the key packages of *glmnet* (65), *metaphor* (71), *caret* (72)*,* *mice* (58), and pmsampsize (55).

This research study was reported in accordance with the TRIPOD statement **(Supplemental table 3)** (73).

[About here link to: Supplemental Table 3 on TRIPOD Checklist: Prediction Model Development and Validation]

**RESULTS**

Of all eligible 4,561 patients from the PROPERmed database for whom multiple imputation datasets were available, 3,582 patients with full data for all candidate prognostic variables were included in the complete-case population (**Figure 1**). In this subset, the HRQoL of 1,046 (29.2 %) patients deteriorated by at least five percent according to the EQ-5D-3L index at six-month follow-up: 105 (27.6 %) patients from PRIMUM, 94 (24.4 %) from Opti-Med, 131 (29.2 %) from PIL, 442 (32.8 %) from ISCOPE and 274 (26.9%) from RIME.

The mean age of the complete-case population was 78 (SD 7) years; 58 % were women, 96 % lived at home, and 88 % had a low/medium level of education. The population had an average of 3 (SD 2) chronic conditions (multimorbidity) and 8 (SD 4) chronic prescriptions (polypharmacy). Seventy-eight percent of patients were taking three or more medications. Sixty-seven percent suffered from pain and 20 % had depressive symptoms.

**Table 1 and Supplemental table 4** show the prognostic variables both overall and stratified according to observed dHRQoL status in the complete-case population. In Supplemental table 5, prognostic variables are shown both overall and stratified according to the interventional status of the original trials in the complete-case population. Supplemental figures 1 and 2 show the baseline HRQoL distribution across countries and study arms.

[About here Figure 1 on Flow chart and schematic course of action]

[About here Table 1 on Prognostic variables and statistically significant univariable associations with dHRQoL]

[About here link to: Supplemental table 4 on Prognostic variables and univariable associations with dHRQoL]

[About here link to: Supplemental table 5 on Candidate prognostic variables and outcome of the five randomized controlled trial stratified by interventional status]

[About here link to: Supplemental figure 1 on Baseline HRQoL distribution across countries]

[About here link to: Supplemental figure 2 on Baseline HRQoL distribution in study arms]

When developing the prognostic model for dHRQoL using the candidates’ prognostic variables, variable selection using LASSO yielded a structural model with the items listed in **Table 2**. Refitting the LASSO-derived model formula to CC, MIM, and MI datasets yielded nearly identical performance metrics in terms of model discrimination (**Figure 2A**) and model calibration (**Figure 2B**). Variable importance metrics illustrated the predictive value of the individual prognostic variables (**Table 2**). Baseline quality of life and functional status showed the greatest prognostic relevance, with a relative contribution to the model’s performance of 62% and 31% respectively (**Figure 2C**). Bootstrap internal validation from **Table 2** yielded an optimism-corrected C-statistic of 0.71 (95 % confidence interval: 0.69 to 0.72) which was close to the C-statistic of 0.72 and indicated good discrimination. An optimism-corrected calibration slope of 0.88 (0.78 to 0.98) indicated moderate calibration. In an explorative analysis, we grouped the prognostic variables according to clinical origin; this process consistently revealed the considerable significance of functional status and well-being to discriminatory performance (**Figure 2D**), while the model derived using variable selection was comparable to full models in internal validation metrics. Between-study heterogeneity was clearly visible in the stratified trial intercepts (**Table 2**). The model performed well for all trials used as validation datasets in the IECV loop, with a pooled C-statistic of 0.68 (0.65 to 0.70), a CITL of 0 (-0.13 to 0.13) (**Figure 3**) and between-study heterogeneity I2 of 24.6 % and 78.6 % respectively. We also obtained a joint probability of 75 % of achieving a C-statistic of 0.65 and CITL between -0.1 and 0.1 in an independent but similar population.

[About here: Table 2 on Final multivariable analysis of dHRQoL at six-month follow-up]

[About here: Figure 2 on model development and validation]

[About here: Figure 3 on meta-analytical summary of IECV loop]

**DISCUSSION**

This is the first IPD-based prognostic model for dHRQoL in a population of older patients with multiple conditions (two or more) and polypharmacy (five or more prescriptions) in general practice. While the prognostic model discriminated well and demonstrated reasonable generalizability in the IECV, intercept recalibration to consider further populations of interest would nevertheless be necessary before implementation. Our model included a wide selection of prognostic variables related to demographics, prescribed medication, potentially inappropriate medication and omissions, functional status, and well-being, which all significantly contributed to the prediction of dHRQoL. Among them, baseline HRQoL (high face validity) was the most important, followed by functional status (well known to be associated with dHRQoL (74)). Simple counts of multimorbidity (30) and polypharmacy did not indicate that patients were at risk per se with regard to dHRQoL, contrary to what is found in the literature (7,75).

Using an IPD-MA to create a model based on primary research data provided a suitable and comprehensive source of information that covered all relevant dimensions that are required in a prognostic model of dHRQoL. The case-mix variability of this database, which includes patients from two different health care contexts and involves a reasonable time frame to avoid limiting external validity, helped us achieve good model performance and promising generalizability. Thus, the IPD framework allowed the generalizability of the prediction model to be estimated, as well as the probability of adequate performance in an independent population. However, the IPD-MA-based modelling approach also entailed the loss of some information (e.g., the smoking status variable was systematically missing, and consideration of common chronic conditions was limited) and made it difficult to clinically interpret some prognostic variables (e.g., standardization of functional status measures). Furthermore, the exclusion criteria of a short life expectancy and dementia limit the generalizability of the findings.

To the best of our knowledge, our dHRQoL prognostic model for older patients with chronic conditions and polypharmacy in general practice is the only one of its kind. Existing risk stratification tools that have been developed and validated to predict negative outcomes in older patients with multiple morbidities have focused mainly on predicting hospital (re-) admissions (76). The C-statistics of these tools varied between 0.5 and 0.85, with the highest C-statistics found in models that included functional status as an outcome (76). Two studies (77,78) that evaluated four risk tools with the aim of identifying people with multiple conditions that were at risk of reduced HRQoL were recently assessed in a NICE guideline review (79). All of these tools demonstrated poor discrimination and calibration in predicting dHRQoL, and their certainty of evidence according to GRADE (80) ranged from low to very low. To date and as far as we are aware, no relevant studies exist that predict dHRQoL in older populations based on polypharmacy or any other medication-related information.

According to the results of the PROPERmed prognostic model, assessment of health-related quality of life and functional status might help physicians to detect patients with multimorbidity and polypharmacy at risk for a potentially preventable deterioration. However, for use in our model, the latter would have to be standardized to take into account mean values and deviation in the target population. Additionally, we recommend using shrunken estimates to multiply the effects of our prognostic variables with the uniform shrinkage factor obtained from internal bootstrap validation. It is also important to consider how best to choose the baseline risk for dHRQoL (intercept) in the new population. While for the original trials an average intercept appeared reasonable for IECV (between-study heterogeneity I2 of 78.6 % in CITL), implementation in a completely new setting may require adjustments to account for outcome frequencies, or even complete re-estimation (17). Therefore, implementation of the PROPERmed dHRQoL model in a completely new setting will require taking the intermediate steps mentioned above, especially as data from the target population is likely to differ from our own. Furthermore, the PROPERmed dHRQoL model should undergo an impact assessment, whereby it is particularly important to evaluate its ability as a prognostic tool to prioritize (complex) interventions in general practice, and thus to determine whether it could actually help optimize medication regimens.

**CONCLUSION**

The first IPD-based prognostic model of dHRQoL in older patients with multiple chronic conditions and medication in general practice performed well in calibration, discrimination and might thus effectively assist in the identification of high-risk patients.

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**AUTHOR CONTRIBUTIONS**

JWB, MvdA, UT, WEH, HJT, PJME, GK, JJM, DKdG, RP, PPG, ADM and CM contributed to the design of the PROPERmed study. CM is the guarantor. AIGG and ADM wrote the first draft of the manuscript. JWB, MvdA, DBL, UT, HR, HJT, PJME and CM represent the five included trials and provided all data needed for the IPD-MA. AIGG and TSD developed the harmonized PROPERmed database; KMAS, HR and BF supported. ADM performed the statistical analysis with the support of RP, KIES and HR. All authors contributed to the manuscript and agreed on its publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria were omitted.

**COMPETING INTEREST**

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any additional organizations for the submitted work; no financial relationships over the past three years with any organizations that might have an interest in the submitted work; no other relationships or activities that could have influenced the submitted work.

**ETHICAL APPROVAL**

The Ethics Commission of the Medical Faculty of the Johann Wolfgang Goethe University, Frankfurt / Main confirmed that no extra vote was necessary for the anonymous use of data from the PROPERmed IPD-MA (13/07/2017). All included trials were separately approved by the relevant ethics commissions as follows:

ISCOPE: The Medical Ethical Committee of Leiden University Medical Center approved the study (date: 30.06.2009, reference: P09.096).

Opti-Med: The Medical Ethics Committee of the VU University Medical Centre Amsterdam approved the study (date: 12.01.2012, reference: 2011/408).

PIL: The Medical Ethics Review Board Atrium-Orbis-Zuyd approved the study (date: 15.12.2009, reference: 09-T-72 NL3037.096.09).

PRIMUM: The Ethics Commission of the Medical Faculty of Johann Wolfgang Goethe University, Frankfurt / Main approved the study (date: 20/05/2010, reference: E 46/10).

RIME: The Ethics Commission of Witten University / Herdecke also approved the study (date: 28.02.2012, reference: 147/2011).

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**Figure legends**

**Figure 1: Flow chart and schematic course of action**

CC = Complete Cases; IPD = Individual Participant Data; LASSO = Least Absolute Shrinkage and Selection Operator; MI = Multiply Imputed; MIM = Missing-Indicator Method; dHRQoL = deterioration in Health-Related Quality of Life.

**Figure 2**: **Model development and validation**. (A) By yielding receiver-operating characteristic (ROC) curves, the model’s estimates of sensitivity and specificity for calculated risks discriminate between patients with and without dHRQoL. ROC curves are visualized for the following study populations: complete cases (CC), one multiply imputed dataset (MI), and data added using the missing-indicator method (MIM). The added lines mark the median risk cut-off of 0.41, with a sensitivity of 72% and specificity of 59%. (B) Similarly, calibration curves are generated by plotting predicted event probabilities against (cumulative) event frequencies. (C) Scrutinizing the impact of model parameters, a variable importance plot highlights their relative contribution to model performance, adjusted in relation to the most important prognostic variable. (D) Exploring the influence of variable origin, we fitted models composed of variables that are sociodemographic and lifestyle-related alone (α), or combinations of α and morbidity-related (β), medication-related (γ) predictors, and / or predictors related to functional status and well-being (δ) in accordance with **Table 1.** Resulting estimates of C-statistics are presented for bootstrap internal validation and internal-external cross-validation (IECV) if all available variables were included into the model (i.e., full model – grey circles) or only those having actually been selected during model development (black circles).

**Figure 3: Meta-analytic summary of model generalizability**.

A bivariate random-effects meta-analysis was conducted to determine the pooled performance metrics of C-statistics and calibration-in-the-large (CITL) from internal-external cross-validation (IECV), with the respective trial serving as the validation set for the model that was refitted in the remaining trials. The Forest plot visualizes trial-specific estimates and their pooled results.

**Supplemental figure 1: Baseline HRQoL distribution across countries.**

Boxplot of HRQoL measurements at baseline on the respective EQ5D scale of the country the original study came from. Distinct values from the original studies are superimposed to highlight between-study variability.

**Supplemental figure 2:; Baseline HRQoL distribution in study arms.**

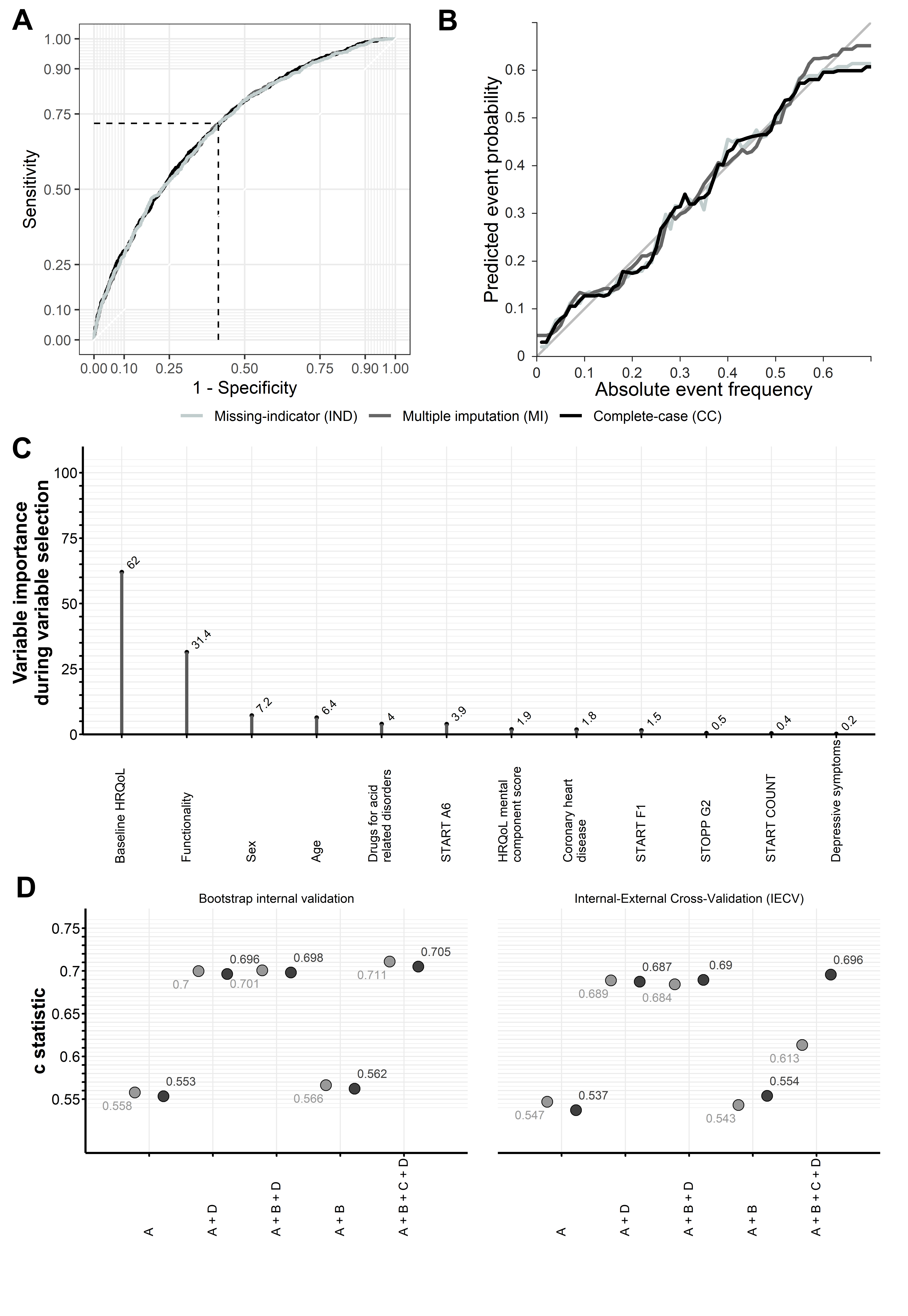
Boxplot of HRQoL measurements at baseline on the respective EQ5D scale of the country the original study came from, according to interventional status. Distinct values from the original studies are superimposed to highlight between-study variability.

**Figure 1**

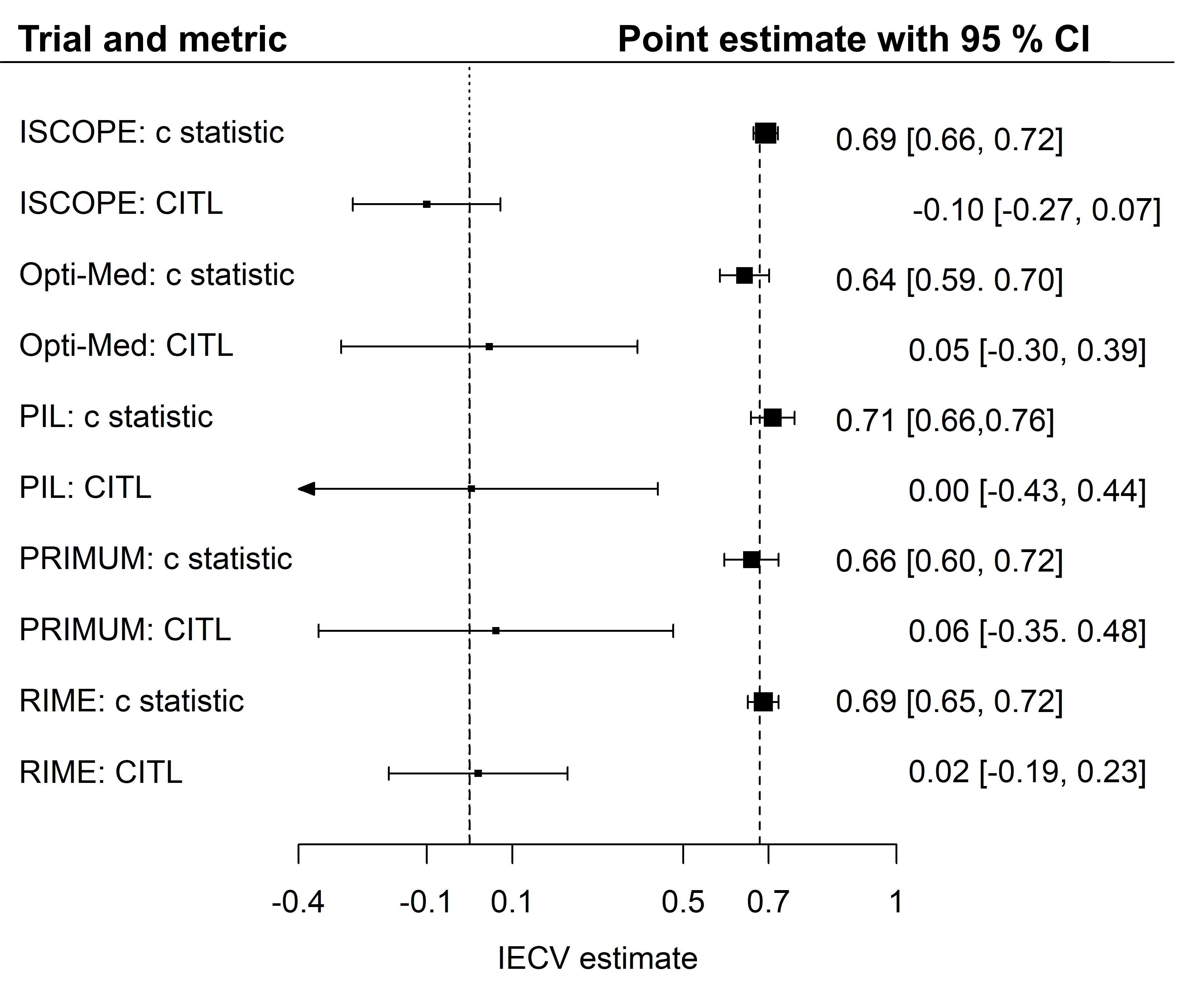
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**Figure 2**



**Figure 3**



**Table 1. Candidate prognostic variables and statistically significant univariable associations with dHRQoL**

|  |  |  |  |
| --- | --- | --- | --- |
| **Candidate prognostic variable** | **dHRQoL (complete-case population)** | | **Descriptive univariable p-value** |
| **No**  **n = 2,536** | **Yes**  **n = 1,046** |
| ***Sociodemographic and lifestyle-related*** |  | | |
| Age - Mean (SD) | 77.2 (6.8) | 78.3 (6.9) | < 0.001 |
| Sex (female) - Frequency (%) | 1,449 (57.1) | 627 (59.9) | 0.122 |
| Living situation (Institutionalized living) - Frequency (%) | 87 (3.4) | 59 (5.6) | 0.003 |
| Educational level - Frequency (%) |  | | |
| - Low | 1,018 (40.1) | 472 (45.1) |  |
| - Medium | 1,206 (47.6) | 469 (44.8) | 0.024 |
| - High | 312 (12.3) | 105 (10.0) | 0.011 |
| ***Morbidity-related*** |  | | |
| Coronary heart disease - Frequency (%) | 817 (32.2) | 393 (37.6) | 0.002 |
| ***Medication-related*** |  | | |
| Drugs for acid-related disorders - Frequency (%) | 950 (68.3) | 441 (31.7) | 0.009 |
| Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD - STOPP G2 - Frequency (%) | 15 (0.6) | 15 (1.4) | 0.015 |
| START criteria\* – Median (IQR) | 1 (2) | 1 (2) | 0.002 |
| START criteria\* (modified) - Frequency (%) | 1,425 (56.2) | 634 (60.6) | 0.015 |
| Heart failure and/or documented coronary artery disease and NO ACE inhibitor - START A6  - Frequency (%) | 255 (10.1) | 160 (15.3) | < 0.001 |
| Ischemic heart disease and NO beta-blocker - START A7 - Frequency (%) | 203 (8.0) | 117 (11.2) | 0.003 |
| Diabetes and NO ACE inhibitor or ARB - START F1 - Frequency (%) | 150 (5.9) | 95 (9.1) | 0.001 |
| ***Functional status and well-being-related*** |  |  |  |
| Functional status – Mean (SD) | -0.123 (0.92) | 0.044 (0.99) | < 0.001 |
| Depression \*\* – Frequency (%) | 485 (19.1) | 201 (19.2) | 0.95 |
| Pain – Frequency (%) | 1,728 (68.1) | 675 (64.5) | 0.037 |
| Health-related quality of life comorbidity index, mental \*\*\* – Median (IQR) | 1 (1) | 1 (1) | 0.044 |

|  |  |  |  |
| --- | --- | --- | --- |
| Quality of life: EQ-5D, version 3L, Index value (baseline) – Mean (SD) | 0.70 (0.26) | 0.81 (0.19) | < 0.001 |

This table shows candidate prognostic variables stratified according to observed dHRQoL status and univariable associations.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; ATC = anatomical therapeutic chemical; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; SD = standard deviation; dHRQoL= deterioration in health-related quality of life.

\* Fifteen START criteria were considered.

\*\*Depression considered possible in case of a positive score on either of the two provided scales (GDS/SF).

\*\*\* Score calculated considering a maximum count of 6 conditions/13 points.

**Table 2. Final multivariable analysis for dHRQoL at six-month follow-up**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Selected prognostic factor** | **System of measurement** | **Estimate\*** | **standard error** | **p value** |
| (Intercept)\*\* |  | -4.457 | 0.581 | 0.000 |
| Age | Years | 0.000 | 0.007 | 0.969 |
| Sex (male) |  | -0.175 | 0.084 | 0.037 |
| Coronary heart disease (Myocardial infarction and/or angina pectoris) - ICPC-2 codes K74, K75, K76 | ICPC-2 codes K74, K75, K76 | 0.216 | 0.094 | 0.022 |
| Drugs for acid-related disorders | ATC code A02 | 0.274 | 0.082 | 0.001 |
| Systemic corticosteroids rather than inhaled corticosteroids for maintenance therapy in moderate-severe COPD - STOPP criteria G2 | (ATC codes H02AB OR H02BX) AND (ICPC-2 codes R79, R95 OR R96) NOT (ATC codes R03BA OR R03AK) | 1.108 | 0.432 | 0.010 |
| START criteria count | 15 START criteria were included | -0.003 | 0.036 | 0.934 |
| ACE inhibitor with heart failure and/or documented coronary artery disease - START criteria A6 | (ICPC-2 codes K74, K75, K76, K77) NOT (ATC codes C09A OR C09B OR C09C OR C09D) | 0.212 | 0.141 | 0.133 |
| ACE inhibitor or ARB (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease i.e. dipstick proteinuria or microalbuminuria - START criteria F1 | (ICPC-2 codes T89 OR T90) NOT (ATC codes C09A OR C09B OR C09C OR C09D) | 0.386 | 0.159 | 0.015 |
| Functional status | Standardized values taken from the VES-13, Katz-15 and GG mobility instruments used in the original studies | 0.557 | 0.053 | 0.000 |
| Depression | Cut-offs for diagnosis of depression taken from the GDS 15/5 or SF12/36 instruments | 0.363 | 0.112 | 0.001 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Mental Component Summary score from health-related quality of life comorbidity index | Score calculated according to the modified instrument: maximum count 6 conditions, 13 points | 0.072 | 0.032 | 0.026 |
| Quality of life: EQ-5D, version 3L, Index value (baseline) | Time Trade-Off values for EQ-5D-3L in German and Dutch populations | 4.175 | 0.263 | 0.000 |

Baseline risks of studies (estimates): RIME -0.136, Opti-Med -0.175, PRIMUM -0.165, PIL 0.000 and ISCOPE 0.476.

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blockers; ATC = anatomical therapeutic chemical; COPD = chronic obstructive pulmonary disease; GDS = geriatric depression scale; GG = geriatric giant; Katz-15; ICPC = international classification of primary care; MCS = Modified health-related quality of life comorbidity index, mental; SF = short form survey; TTO = time trade-off; VES = vulnerable elders survey; dHRQoL= deterioration in health-related quality of life.

\*Estimate = Parameter estimate of the maximum-likelihood fitted logistic regression model (possibly to be multiplied with the uniform shrinkage factor of 0.88).

\*\*Intercept = Overall baseline risk for dHRQoL.

\*\*\*Depression considered possible in case of a positive score on either of the two provided scales (GDS/SF).

**Supplemental Table 1. Main characteristics of the included trials**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **PRIMUM** | **Opti-Med** | **PIL** | **ISCOPE** | **RIME** |
| **Title** | PRIoritizing MUltimedication in Multimorbidity | Optimized clinical Medication reviews in older people | Polypharmacy intervention in Limburg | Integrated  Care for Older People | Reduction of potentially inadequate Medication in the Elderly |
| **Study region** | Hesse, Germany | Amsterdam, The Netherlands | Southern Limburg, The Netherlands | Leiden, The Netherlands | Witten and Hanover, Germany |
| **Start/End** | 2010-2012 | 2013-2015 | 2010-2014 | 2009-2011 | 2012-2014 |
| **Design** | 2-arm parallel cRCT | 2-arm parallel cRCT | 2-arm parallel cRCT, stepped wedge | 2-arm parallel cRCT | 2-arm parallel cRCT |
| **Setting** | General practices (n=72) | General practices (n=22) | General practices (n=24) | General practices (n=51) | General practices (n=139) |
| **Study population** | N=502  ≥60 years  ≥5 chronic prescriptions  ≥3 chronic conditions | N=518  ≥65 years  ≥1 chronic prescription Geriatric giant | N=727  ≥60 years  ≥5 chronic prescriptions | N=1,617  ≥75 years  Complex problems on ≥3  domains | N=1,197  ≥6 chronic prescriptions |
| **Exclusion criteria** | Life expectancy of ≤12  months  Abuse of alcohol or illegal drugs  Inability to fill in questionnaires and to participate in telephone interviews  Dementia | Life expectancy of ≤6 months Severe psychiatric illness or other reasons why GP regards patient as unable to participate  Recent medication review (last 6 months)  Dementia | Life expectancy of ≤12  months  Abuse of alcohol or illegal drugs  Dementia | Life expectancy of ≤3 months or terminal illness  Dementia | Life expectancy of ≤6 months as assessed by the treating GP  Dementia |
| **Intervention** | Structured medication review including several intervention components (complex intervention) | Structured medication review including several intervention components (complex intervention) | Structured medication review including several intervention components (complex intervention) | Integrated care plan using a functional geriatric approach | Structured medication review including several intervention components (complex intervention) |
| **Data collection (study visits)** | 0, 6, 9 months | 0, 3, 6 months | 0, 3, 6, 12 months | 0, 6, 12 months | 0, 6, 12 months |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Data collection (method)** | CRF, patient questionnaire, telephone interview | CRF, patient questionnaire | CRF, patient questionnaire, home visit | Patient questionnaire, home visit | CRF, patient questionnaire, telephone interview |

cRCT= Cluster-Randomized Controlled Trial; CRF = Case Report Form

**Supplemental Table 2. Prognostic variables and their definitions**

|  |  |  |
| --- | --- | --- |
| **Candidate prognostic variable** | **Type of variable** | **Categories** |
| *Sociodemographic and lifestyle-related* | | |
| Age | Continuous |  |
| Sex | Binary | Male / female |
| Living situation | Binary | At home / institutionalized |
| Educational level | Quasi-continuous |  |
| Smoking status | Categorical | Smoker / ex-smoker / non-smoker |
| *Morbidity-related* | | |
| Single conditions (n = 15)   * Cancer * Cerebrovascular disease * Chronic obstructive pulmonary disease / asthma * Coronary heart disease * Depression * Diabetes * Hearing problems * Heart failure * HIV infection /AIDS * Hypertension * Osteoarthritis * Osteoporosis * Parkinsonism * Rheumatoid / seropositive arthritis * Vision problems | Binary | Yes / No |
| Disease count according to Diederichs list | Continuous |  |
| Charlson comorbidity index | Continuous |  |
| *Medication-related* | | |
| No. of drugs | Continuous |  |
| Polypharmacy ( 5 drugs) | Binary | Yes / No |
| 3-digit ATC-codes | Binary | Yes / No |
| Potentially Inappropriate Medications (PIM) according to the EU-PIM list | Continuous |  |
| Binary | Yes / No |
| Drug Burden Index (DBI) | Continuous |  |
| Binary | Yes / No |
| Anticholinergic Drug Burden (ADB) according to Durán | Continuous |  |
| Binary | Yes / No |
| Anticholinergic Drug Scale (ADS) according to Carnahan | Continuous |  |
| Binary | Yes / No |
| STOPP criteria | Continuous |  |
| Binary | Yes / No |

|  |  |  |
| --- | --- | --- |
| STOPP criteria – single items (B1-B3, B10, B12, B13, C6, C7, C10, C11, D2, D5-D7, D14, F1, G1, G2, H2-H5, H7, H8, J1-J3, K1-K4, M1) | Binary | Yes / No |
| Dreischulte criteria | Continuous |  |
| Binary | Yes / No |
| Dreischulte criteria – single items (A1-A6, B1, B3) | Binary | Yes / No |
| START criteria | Continuous |  |
| Binary | Yes / No |
| START criteria – single items (A3, A5-A8, B1, B2, C1, C2, E1-E4, E7, F1) | Binary | Yes / No |
| *Functional status and well-being related* | | |
| Functional status according to VES-13, Katz- 15, and GG mobility | Continuous |  |
| Depression according to GDS 5, GDS 15, SF 12,  SF 36 | Continuous |  |
| Binary | Yes / No |
| Binary | Yes / No |
| Pain according to von Korff, SF 12, SF 36 | Continuous |  |
| Binary | Yes / No |
| Health-related quality of life comorbidity index, mental | Continuous |  |
| Health-related quality of life comorbidity index, physical | Continuous |  |
| Quality of life: EQ-5D, version 3L, Index value | Continuous |  |
| Hospital admissions | Continuous |  |

**Supplemental Table 3. TRIPOD statement**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Section/Topic m Checklist Item Page** | | | | |
| **Title and abstract** | | | | |
| Title | 1 | D;V | Identifies the study as developing and/or validating a multivariable prediction model; mentions the target population, and the outcome to be predicted. | 1 |
| Abstract | 2 | D;V | Provides a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. | 4 |
| **Introduction** | | | | |
| Background and objectives | 3a | D;V | Explains the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | 7-8 |
| 3b | D;V | Specifies the objectives, including whether the study describes the development or validation of the model or both. | 8 |
| **Methods** | | | | |
| Source of data | 4a | D;V | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation datasets, if applicable. | 8 |
| 4b | D;V | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. | 8 |
| Participants | 5a | D;V | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centers. | 8,9 |
| 5b | D;V | Describe eligibility criteria for participants. | 9 |
| 5c | D;V | Give details of treatments received, if relevant. | n/a |
| Outcome | 6a | D;V | Clearly define the outcome that is predicted by the model, including how and when assessed. | 9 |
| 6b | D;V | Report any blinded assessments of the outcome to be predicted. | n/a |
| Predictors | 7a | D;V | Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured. | 9-11 |
| 7b | D;V | Report any blinded assessments of predictors for the outcomes and other predictors. | n/a |
| Sample size | 8 | D;V | Explain how the study size was arrived at. | 11 |
| Missing data | 9 | D;V | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. | 11,12 |
| Statistical analysis methods | 10a | D | Describe how predictors were handled in the analyses. | 12-14 |
| 10b | D | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. | 12-14 |
| 10c | V | Describe how predictions were calculated for validation. | 12-14 |
| 10d | D;V | Specify all measures used to assess model performance and, if relevant, to compare multiple models. | 12-14 |
| 10e | V | Describe any model updating (e.g., recalibration) arising from the validation. | 12-14 |
| Risk groups | 11 | D;V | Provide any details on how risk groups were created. | n/a |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Develop- ment vs. validation | 12 | V | Identify any differences from the development data in setting, eligibility criteria, outcome, and predictors for use in validation. | 12-14 |
| **Results** | | | | |
| Participants | 13a | D;V | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, provide a summary of the follow-up period. A diagram may be helpful. | 14 (Figure  1) |
| 13b | D;V | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome. | 14,15  (Table 1, Supp table 4) |
| 13c | V | Show a comparison of the distribution of important variables with the development data (demographics, predictors and outcomes) for validation purposes. | n/a |
| Model develop- ment | 14a | D | Specify the number of participants and outcome events in each analysis. | 14  (Figure 1) |
| 14b | D | Report any unadjusted association between each candidate, predictor and outcome. | Table 1, Supplem entary table 4) |
| Model specifica- tion | 15a | D | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point). | 15, 16  (Table 2) |
| 15b | D | Explain how to use the prediction model. | Table 2 |
| Model perfor- mance | 16 | D;V | Report performance measures (with CIs) for the prediction model. | 15,16(Fig  ures 2  and 3) |
| Model- update | 17 | V | Report on any model update (i.e., model specification, model performance). | n/a |
| **Discussion** | | | | |
| Limitations | 18 | D;V | Mentions limitations of the study (such as non-representative sample, few events per predictor, missing data). | 16-18 |
| Interpreta- tion | 19a | V | Mentions the results with reference to performance in the development data, and any other validation data. | 16-18 |
| 19b | D;V | Gives an overall interpretation of the results, and considers objectives, limitations, results from similar studies, and other relevant evidence. | 16-18 |
| Implications | 20 | D;V | Discusses the potential clinical use of the model and implications for future research. | 18 |
| **Other information** | | | | |
| Supple- mentary information | 21 | D;V | Provides information on the availability of supplementary resources, such as study protocol, web calculator, and datasets. | 8  (Supple- mentary table 1) |
| Funding | 22 | D;V | Gives the source of funding and the role of the funders for the present study. | 19 |

n/a = not applicable

\*Items relevant only to the development of a prediction model are denoted by D, items related solely to a validation of a prediction model are denoted by V, and items related to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

**Supplemental Table 4. Candidate prognostic variables and univariable associations with dHRQoL**

|  |  |  |  |
| --- | --- | --- | --- |
| **Candidate prognostic variable** | **dHRQoL (complete-case population)** | | **Descriptive univariable p-value** |
| **Sociodemographic and lifestyle-related** | **No**  **n = 2,536** | **Yes**  **n = 1,046** |  |
| Age - Mean (SD) | 77.2 (6.8) | 78.3 (6.9) | < 0.001 |
| Sex (female) - Frequency (%) | 1,449 (57.1) | 627 (59.9) | 0.122 |
| Living situation (Institutionalized living) - Frequency (%) | 87 (3.4) | 59 (5.6) | 0.003 |
| Educational level - Frequency (%) |  |  |  |
| - Low | 1,018 (40.1) | 472 (45.1) |  |
| - Medium | 1,206 (47.6) | 469 (44.8) | 0.024 |
| - High | 312 (12.3) | 105 (10.0) | 0.011 |
| **Morbidity-related** |  |  |  |
| Single conditions - Frequency (%) |  |  |  |
| - Cancer | 471 (18.6) | 191 (18.3) | 0.827 |
| - Cerebrovascular disease | 401 (15.8) | 165 (15.8) | 0.977 |
| - Chronic obstructive pulmonary disease / asthma | 494 (19.5) | 221 (21.1) | 0.262 |
| - Coronary heart disease | 817 (32.2) | 393 (37.6) | 0.002 |
| - Diabetes | 885 (34.9) | 377 (36.0) | 0.514 |
| - Hearing problems | 511 (20.2) | 207 (19.8) | 0.807 |
| - Heart failure | 435 (17.2) | 197 (18.8) | 0.23 |
| - Hypertension | 1,726 (68.1) | 683 (65.3) | 0.109 |
| - Osteoarthritis | 863 (34.0) | 338 (32.3) | 0.323 |
| - Osteoporosis | 390 (15.4) | 156 (14.9) | 0.725 |
| - Parkinsonism | 53 (2.1) | 25 (2.4) | 0.576 |
| - Rheumatoid arthritis | 219 (8.6) | 97 (9.3) | 0.541 |
| - Vision problems | 804 (31.7) | 338 (32.3) | 0.722 |
| Disease count according to Diederichs list \* – Median (IQR) | 3 (2) | 3 (2) | 0.191 |

|  |  |  |  |
| --- | --- | --- | --- |
| **Medication-related** |  |  |  |
| No. of drugs† - Median (IQR) | 7 (5) | 7 (5) | 0.720 |
| Polypharmacy ( 5 drugs) - Frequency (%) | 1,978 (78.0) | 808 (77.3) | 0.623 |
| 3-digit ATC-codes - Frequency (%) |  |  |  |
| - Drugs for acid-related disorders - A02 | 950 (68.3) | 441 (31.7) | 0.009 |
| - Drugs for constipation - A06 | 220 (71.7) | 87 (28.3) | 0.728 |
| - Drugs used in diabetes - A10 | 718 (70.0) | 308 (30.0) | 0.495 |
| - Mineral supplements - A12 | 452 (72.3) | 173 (27.7) | 0.357 |
| - Antithrombotic agents - B01 | 1,602 (70.3) | 677 (29.7) | 0.380 |
| - Cardiac therapy - C01 | 566 (68.4) | 261 (31.6) | 0.089 |
| - Diuretics - C03 | 1,024 (69.1) | 457 (30.9) | 0.067 |
| - Beta blocking agents - C07 | 1,369 (71.4) | 549 (28.6) | 0.414 |
| - Calcium channel blockers - C08 | 752 (72.8) | 281 (27.2) | 0.094 |
| - Agents acting on the renin–angiotensin system - C09 | 1,625 (71.8) | 637 (28.2) | 0.073 |
| - Lipid-modifying agents- C10 | 1,346 (70.8) | 555 (29.2) | 0.993 |
| - Urologicals - G04 | 328 (70.5) | 137 (29.5) | 0.895 |
| - Thyroid therapy - H03 | 412 (71.8) | 162 (28.2) | 0.574 |
| - Anti-inflammatory and antirheumatic products - M01 | 316 (70.5) | 132 (29.5) | 0.896 |
| - Antigout preparations - M04 | 302 (73.9) | 112 (27.0) | 0.307 |
| - Analgesics - N02 | 441 (71.9) | 172 (28.1) | 0.494 |
| - Psycholeptics - N05 | 357 (68.3) | 166 (31.7) | 0.167 |
| - Psychoanaleptics - N06 | 332 (71.7) | 131 (28.3) | 0.645 |
| - Drugs for obstructive airway diseases - R03 | 414 (69.7) | 180 (30.3) | 0.518 |
| - Ophthalmologicals - S01 | 418 (71.7) | 165 (28.3) | 0.602 |
| - Cardiac therapy - C01 | 566 (68.4) | 261 (31.6) | 0.089 |
| No. of Potentially Inappropriate Medications (PIM) according to the EU-PIM list - Median (IQR) | 1 (1) | 1 (1) | 0.945 |
| Drug Burden Index (DBI) - Median (IQR) | 0 | 0 | 0.929 |
| Anticholinergic Drug Burden (ADB) according to Duran - Median (IQR) | 0 | 0 | 0.826 |
| Anticholinergic Drug Scale (ADS) according to Carnahan - Median (IQR) | 0 | 1 (0) | 0.086 |
| Overuse |  |  |  |

|  |  |  |  |
| --- | --- | --- | --- |
| - STOPP criteria \*\* – Median (IQR) | 1 (1) | 1 (1) | 0.459 |
| - STOPP criteria \*\* - Frequency (%) | 2,164 (85.3) | 884 (84.5) | 0.532 |
| - Verapamil or diltiazem with heart failure - STOPP B2 | 23 (0.9) | 13 (1.2) | 0.361 |
| - Aldosterone antagonists (e.g. spironolactone, eplerenone) with concurrent potassium- conserving drugs (e.g. ACE inhibitors, ARBs, amiloride, or triamterene) - STOPP B12 | 85 (3.4) | 38 (3.6) | 0.674 |
| - Antiplatelet agents such as vitamin K antagonists, direct thrombin inhibitors, or factor Xa inhibitors in patients with coronary or cerebrovascular disease - STOPP C6 | 25 (1.0) | 16 (1.5) | 0.205 |
| - NSAID and vitamin K antagonists, direct thrombin inhibitors, or factor Xa inhibitors in combination - STOPP C10 | 45 (1.8) | 21 (2.0) | 0.637 |
| - NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis - STOPP C11 | 66 (2.6) | 33 (3.2) | 0.360 |
| - Benzodiazepines - STOPP D5 and K1 | 274 (10.8) | 122 (11.7) | 0.456 |
| - Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD - STOPP G2 | 15 (0.6) | 15 (1.4) | 0.015 |
| - NSAID with hypertension or heart failure - STOPP H2 | 69 (2.7) | 41 (3.9) | 0.060 |
| - NSAID for symptom relief of osteoarthritis pain - STOPP H3 | 184 (7.3) | 75 (7.2) | 0.929 |
| - Corticosteroids (other than periodic intra-articular injections for mono-articular pain) for osteoarthritis - STOPP H5 | 69 (2.7) | 29 (2.8) | 0.931 |
| - NSAID with concurrent corticosteroids without PPI prophylaxis - STOPP H8 | 5 (0.2) | 3 (0.3) | 0.607 |
| - Thiazolidenediones (e.g. rosiglitazone, pioglitazone) in patients with heart failure - STOPP J2 | 2 (0.1) | 1 (0.1) | 0.875 |
| - Beta-blockers in diabetes mellitus - STOPP J3 | 501 (19.8) | 217 (20.8) | 0.501 |
| - Neuroleptic drugs - STOPP K2 | 24 (0.9) | 13 (1.2) | 0.426 |
| - Vasodilator drugs (e.g. alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers) - STOPP K3 | 1,868 (73.7) | 760 (28.9) | 0.538 |
| - Hypnotic Z-drugs e.g. zopiclone, zolpidem, zaleplon - STOPP K4 | 59 (2.3) | 33 (3.2) | 0.156 |
| - Dreischulte criteria \*\*\* - Median (IQR) | 0 | 0 | 0.781 |
| - Dreischulte criteria \*\*\* - Frequency (%) | 222 (8.8) | 91 (8.7) | 0.958 |
| - Prescribed a traditional oral NSAID or low dose aspirin but NO gastro-protective drug - Dreischulte A1 | 160 (6.3) | 65 (6.2) | 0.915 |
| - Prescribed a traditional oral NSAID but NO gastro-protective drug (aged ≥ 75 years)- Dreischulte A2 | 80 (3.2) | 35 (3.3) | 0.768 |

|  |  |  |  |
| --- | --- | --- | --- |
| - Prescribed both a diuretic and an ACE inhibitor/ARB and prescribed any oral NSAID - Dreischulte B1 | 82 (3.2) | 37 (3.5) | 0.645 |
| - Heart failure and prescribed any oral NSAID - Dreischulte B3 | 57 (2.3) | 26 (2.5) | 0.667 |
| Underuse |  |  |  |
| - START criteria\*\*\*\* – Median (IQR) | 1 (2) | 1 (2) | 0.002 |
| - START criteria\*\*\*\* - Frequency (%) | 1,425 (56.2) | 634 (60.6) | 0.015 |
| - Documented history of coronary or cerebral vascular disease with NO antiplatelet therapy (aspirin, clopidogrel, prasugrel, or ticagrelor) - START A3 | 307 (12.1) | 115 (11.0) | 0.348 |
| - Documented history of coronary or cerebral vascular disease (Aged 85 years and under) but NO statin therapy - START A5 | 256 (10.1) | 123 (11.8) | 0.141 |
| - Heart failure and/or documented coronary artery disease but NO ACE inhibitor - START A6 | 255 (10.1) | 160 (15.3) | < 0.001 |
| - Ischemic heart disease but NO beta-blocker - START A7 | 203 (8.0) | 117 (11.2) | 0.003 |
| - Heart failure but NO appropriate beta-blocker (bisoprolol, nebivolol, metoprolol or carvedilol) - START A8 | 153 (6.0) | 75 (7.2) | 0.206 |
| - Asthma or COPD but NO inhaled b2 agonist or antimuscarinic bronchodilator (e.g. ipratropium, tiotropium) - START B1 | 263 (10.4) | 108 (10.3) | 0.968 |
| - Asthma or COPD but NO regular inhaled corticosteroid - START B2 | 377 (14.9) | 172 (16.4) | 0.234 |
| - Presence of depressive symptoms but NO Non-TCA antidepressant drug - START C2 | 92 (3.6) | 51 (4.9) | 0.084 |
| - Patients taking long-term systemic corticosteroid therapy but NO bisphosphonates and vitamin D and calcium - START E2 | 94 (3.7) | 53 (5.1) | 0.063 |
| - Patients with known osteoporosis but NO Vitamin D and calcium supplement - START E3 | 199 (7.9) | 78 (7.5) | 0.691 |
| - Patients with documented osteoporosis but NO bone anti-resorptive or anabolic therapy (e.g. bisphosphonate, strontium ranelate, teriparatide, or denosumab) - START E4 | 257 (10.1) | 98 (9.4) | 0.486 |
| - Patients taking methotrexate but NO folic acid supplement - START E7 | 56 (2.2) | 25 (2.4) | 0.739 |
| - Diabetes but NO ACE inhibitor or ARB - START F1 | 150 (5.9) | 95 (9.1) | 0.001 |
| **Functional status and well-being-related** |  |  |  |
| Functional status – Mean (SD) | -0.123 (0.92) | 0.044 (0.99) | < 0.001 |
| Depression \*\*\*\*\* – Frequency (%) | 485 (19.1) | 201 (19.2) | 0.95 |
| Pain – Frequency (%) | 1,728 (68.1) | 675 (64.5) | 0.037 |
| Health-related quality of life comorbidity index, mental \*\*\*\*\*\*– Median (IQR) | 1 (1) | 1 (1) | 0.044 |

|  |  |  |  |
| --- | --- | --- | --- |
| Health-related quality of life comorbidity index, physical \*\*\*\*\*\*\*– Median (IQR) | 5 (4) | 5 (4) | 0.1 |
| Quality of life: EQ-5D, version 3L, Index value (baseline) – Mean (SD) | 0.70 (0.26) | 0.81 (0.19) | < 0.001 |
| **Group assigned** |  |  |  |
| - Control – Frequency (%) | 1,143 (45.07) | 465 (44.46) |  |
| - Intervention – Frequency (%) | 1,393 (54.97) | 581 (55.54) | 0.736 |

This table shows candidate prognostic variables stratified according to observed dHRQoL status and univariable associations.

ACE = angiotensin converting enzyme; ARB = angiotensin II receptor blockers; ATC = anatomical therapeutic chemical; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; No. = number; NSAID = nonsteroidal anti-inflammatory drugs; PPI = proton-pump inhibitor; SD = standard deviation; TCA = tricyclic antidepressants; dHRQoL= deterioration in health-related quality of life.

\*Twelve conditions were considered over a total of 17 conditions included in the Diederichs list.

\*\*Thirty-two STOPP criteria were considered.

\*\*\*Eight Dreischulte criteria were considered.

\*\*\*\*Fifteen START criteria were considered.

\*\*\*\*\*Depression considered possible in case of a positive score on either of the two provided scales (GDS/SF).

\*\*\*\*\*\*Score calculated considering a maximum count of six conditions. Score calculated considering a maximum count of 12 conditions.

\*\*\*\*\*\*\*Score calculated considering a maximum count

**Supplemental Table 5. Candidate prognostic variables and outcome of the five randomized controlled trials stratified by interventional status**

**Candidate prognostic variables – Sociodemographic and lifestyle-related (baseline)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **PRIMUM** | | **Opti-Med** | | **PIL** | **ISCOPE** | | **RIME** | |
| CG  n = 190 | IG  n = 191 | CG  n = 191 | IG  n = 195 | Stepped-wedge design n = 448 | CG  n = 722 | IG  n = 626 | CG  n = 505 | IG  n = 514 |
| Age – Mean (SD) | 71.44 (7.3) | 72.47 (6.5) | 76.9 (8.0) | 76.9 (7.4) | 72.4 (7.4) | 82.00 (5.0) | 81.34 (5.0) | 76.7 (4.7) | 76.8 (5.0) |
| Sex (female) - Frequency (%) | 98 (51.6) | 88 (46.1%) | 63 (33.0%) | 72 (36.9%) | 245 (54.7%) | 214 (29.6%) | 209 (33.4%) | 269 (53.3%) | 248 (48.2%) |
| Living situation (Institutionalized living) - Frequency (%) | 1 (0.5%) | 0 (0.0%) | 4 (2.1%) | 1 (0.5%) | 13 (2.9%) | 54 (7.5%) | 36 (5.8%) | 17 (3.4%) | 20 (3.9%) |
| Educational level - Frequency (%) |  |  |  |  |  |  |  |  |  |
| - Low | 104 (54.7%) | 127  (66.5%) | 38 (19.9%) | 47 (24.1%) | 308 (68.8%) | 364 (50.4) | 323 (51.6%) | 95 (18.8%) | 84 (16.3%) |
| - Medium | 66 (34.7%) | 51 (26.7%) | 89 (46.6%) | 88 (45.1%) | 86 (19.2%) | 297 (41.1) | 245 (39.1%) | 364 (72.1%) | 389 (75.7%) |
| - High | 20 (10.5%) | 13 (6.8%) | 64 (33.5%) | 60 (30.8%) | 54 (12.1%) | 61 (8.4) | 58 (9.3%) | 46 (9.1%) | 41 (8.0%) |

**Candidate prognostic variables – Morbidity-related (baseline)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **PRIMUM** | | **Opti-Med** | | **PIL** | **ISCOPE** | | **RIME** | |
| CG  n = 190 | IG  n = 191 | CG  n = 191 | IG  n = 195 | Stepped-wedge design n = 448 | No  n = 722 | Yes  n = 626 | No  n = 505 | Yes  n = 514 |
| Single conditions - Frequency (%) |  |  |  |  |  |  |  |  |  |
| - Cancer | 21 (11.1%) | 12 (6.3% | 58 (30.4%) | 49 (25.1%) | 60 (13.4%) | 158 (21.9%) | 109 (17.4%) | 77 (15.2%) | 118 (23.0%) |
| - Cerebrovascular disease | 41 (21.6%) | 30 (15.7%) | 29 (15.2%) | 32 (16.4%) | 68 (15.2%) | 123 (17.0%) | 104 (16.6%) | 65 (12.9%) | 74 (14.4%) |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| - Chronic obstructive pulmonary disease / asthma | 50 (26.3%) | 52 (27.2%) | 37 (19.4%) | 41 (21.0%) | 77 (17.2%) | 121 (16.8%) | 115 (18.4%) | 127 (25.1% | 95 (18.5%) |
| - Coronary heart disease | 85 (44.7%) | 75 (39.3%) | 45 (23.6%) | 47 (24.1%) | 190 (42.4%) | 191 (26.5%) | 138 (22.0%) | 227 (45.0%) | 212 (41.2%) |
| - Diabetes | 103 (54.2%) | 100 (52.4%) | 34 (17.8%) | 55 (28.2%) | 182 (40.6%) | 157 (21.7%) | 176 (28.1%) |  |  |
| - Hearing problems | 2 (1.1%) | 9 (4.7%) | 19 (9.9%) | 14 (7.2%) | 59 (13.2%) | 128 (17.7%) | 84 (13.4%) | 205 (40.6%) | 198 (38.5%) |
| - Heart failure | 33 (17.4%) | 30 (15.7%) | 21 (11.0%) | 16 (8.2%) | 34 (7.6%) | 81 (11.2%) | 81 (12.9%) | 171 (33.9%) | 165 (32.1%) |
| - Hypertension | 162 (85.3%) | 160 (83.8%) | 109 (57.1%) | 111 (56.9%) | 290 (64.7%) | 381 (52.8%) | 295 (47.1%) | 441 (87.3%) | 460 (89.5%) |
| - Osteoarthritis | 89 (46.8%) | 114 (59.7%) | 63 (33.0%) | 55 (28.2%) | 114 (25.4%) | 179 (24.8%) | 133 (21.2%) | 218 (43.2%) | 236 (45.9%) |
| - Osteoporosis | 19 (10.0%) | 23 (12.0%) | 44 (23.0%) | 34 (17.4%) | 73 (16.3%) | 79 (10.9%) | 64 (10.2%) | 104 (20.6%) | 106 (20.6%) |
| - Parkinsonism | 4 (2.1%) | 1 (0.5%) | 10 (5.2%) | 3 (1.5%) | 3 (0.7%) | 22 (3.0%) | 13 (2.1%) | 7 (1.4%) | 15 (2.9%) |
| - Rheumatoid arthritis | 12 (6.3%) | 12 (6.3%) | 8 (4.2%) | 3 (1.5%) | 31 (6.9%) | 33 (4.6%) | 22 (3.5%) | 97 (19.2%) | 98 (19.1%) |
| - Vision problems | 26 (13.7%) | 34 (17.8%) | 72 (37.7%) | 68 (34.9%) | 121 (27.0%) | 187 (25.9%) | 159 (25.4%) | 224 (44.4%) | 251 (48.8%) |
| Disease count according to Diederichs list – Median (IQR) | 4 (4) | 4 (3) | 3 (5) | 3 (5) | 3 (3) | 3 (5) | 2 (5) | 4 (4) | 4 (4) |

**Candidate prognostic variables – Medication-related (baseline)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **PRIMUM** | | **Opti-Med** | | **PIL** | **ISCOPE** | | **RIME** | |
| CG  n = 190 | IG  n = 191 | CG  n = 191 | IG  n = 195 | Stepped-wedge design n = 448 | CG  n = 722 | IG  n = 626 | CG  n = 505 | IG  n = 514 |
| No. of drugs† - Median (IQR) | 9 (4) | 8 (3) | 5 (5) | 5 (5) | 7 (3) | 5 (5) | 5 (5) | 9 (4) | 9 (4) |
| No. of Potentially Inappropriate Medications (PIM) according to the EU-PIM list - Median (IQR) | 1 (2) | 1 (1) | 1 (1) | 1 (1) | 1 (2) | 1 (1) | 1 (1) | 1 (2) | 1 (2) |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Drug Burden Index (DBI)  - Median (IQR) | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 0 (1) |
| Anticholinergic Drug Burden (ADB) according to Duran - Median (IQR) | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 0 (1) |
| Anticholinergic Drug Scale (ADS) according to Carnahan - Median (IQR) | 0 (1) | 0 (1) | 0 (1) | 0 (1) | 1 (1) | 0.5 (1) | 0 (1) | 0 (1) | 0.5 (1) |
| STOPP criteria (modified)  – Median (IQR) | 2 (2) | 2 (2) | 1 (2) | 1 (2) | 1 (1) | 1 (2) | 1 (2) | 2 (2) | 2 (2) |
| Dreischulte criteria (modified) - Median (IQR) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| START criteria (modified)  – Median (IQR) | 1 (2) | 1 (2) | 0 (2) | 0 (1) | 1 (2) | 1 (2) | 1 (2) | 1 (2) | 1 (2) |

**Candidate prognostic variables – Functional status and well-being-related (baseline)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **PRIMUM** | | **Opti-Med** | | **PIL** | **ISCOPE** | | **RIME** | |
| CG  n = 190 | IG  n = 191 | CG  n = 191 | IG  n = 195 | Stepped-wedge design n = 448 | CG  n = 722 | IG  n = 626 | CG  n = 505 | IG  n = 514 |
| Functional status – Mean (SD) | -0.07 (1.0) a | -0.1 (0.9) a | -0.03 (1.00) b | -0.05  (1.02) b | -0.10 (0.91) c | -0.04 (0.95) c | -0.13 (0.86) c | -0.1 (0.99) a | -0.03 (0.96)a |
| Depression††– Frequency (%) | 21 (11.1%) d | 29 (15.2%)  d | 61 (31.9%) e | 54 (27.7%)  e | 17 (3.8%) e | 115 (15.9%) d | 92 (14.7%) d | 140 (27.7%)  d | 157 (30.5%)  d |
| Pain – Frequency (%) | 164 (86.3%) f | 172  (90.1%) f | 146 (76.4%)  g | 145  (74.4%) g | 351 (78.3%) h | 367 (50.8%) i | 313 (50.0%)  i | 359 (71.1%)  h | 386 (75.1) h |
| Health-related quality of life comorbidity index, mental – Median (IQR) | 1 (3) | 1 (2) | 0 (1) | 0 (1) | 1 (1) | 0 (1) | 0 (1) | 1 (3) | 1 (2) |
| Health-related quality of life comorbidity index, physical – Median (IQR) | 6 (6) | 5 (5) | 3 (4) | 3 (4) | 4 (4) | 3 (4) | 3 (4) | 7 (6) | 7 (6) |

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Quality of life: EQ-5D, version 3L, Index value (baseline) – Mean (SD) | 0.8 (0.2) | 0.8 (0.2) | 0.8 (0.2) | 0.7 (0.2) | 0.8 (0.2) j | 0.69 (0.26) j | 0.69 (0.27) j | 0.73 (0.27) | 0.75 (0.24) |

**Candidate prognostic variables – Quality of life (6-month follow-up)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Variables** | **PRIMUM** | | **Opti-Med** | | **PIL** | **ISCOPE** | | **RIME** | |
| CG  n = 190 | IG  n = 191 | CG  n = 191 | IG  n = 195 | Stepped-wedge design n = 448 | CG  n = 722 | IG  n = 626 | CG  n = 505 | IG  n = 514 |
| dHRQoL – Frequency (%) | 50 (26.3%) | 55 (28.8%) | 51 (26.7%) | 43 (22.1%) | 131 (29.2%) j | 240 (33.2%) | 202 (32.3%) | 124 (24.6%) | 150 (29.2%) |

CG = control group; dHRQoL= deterioration in health-related quality of life; IG = intervention group; NA = not available.

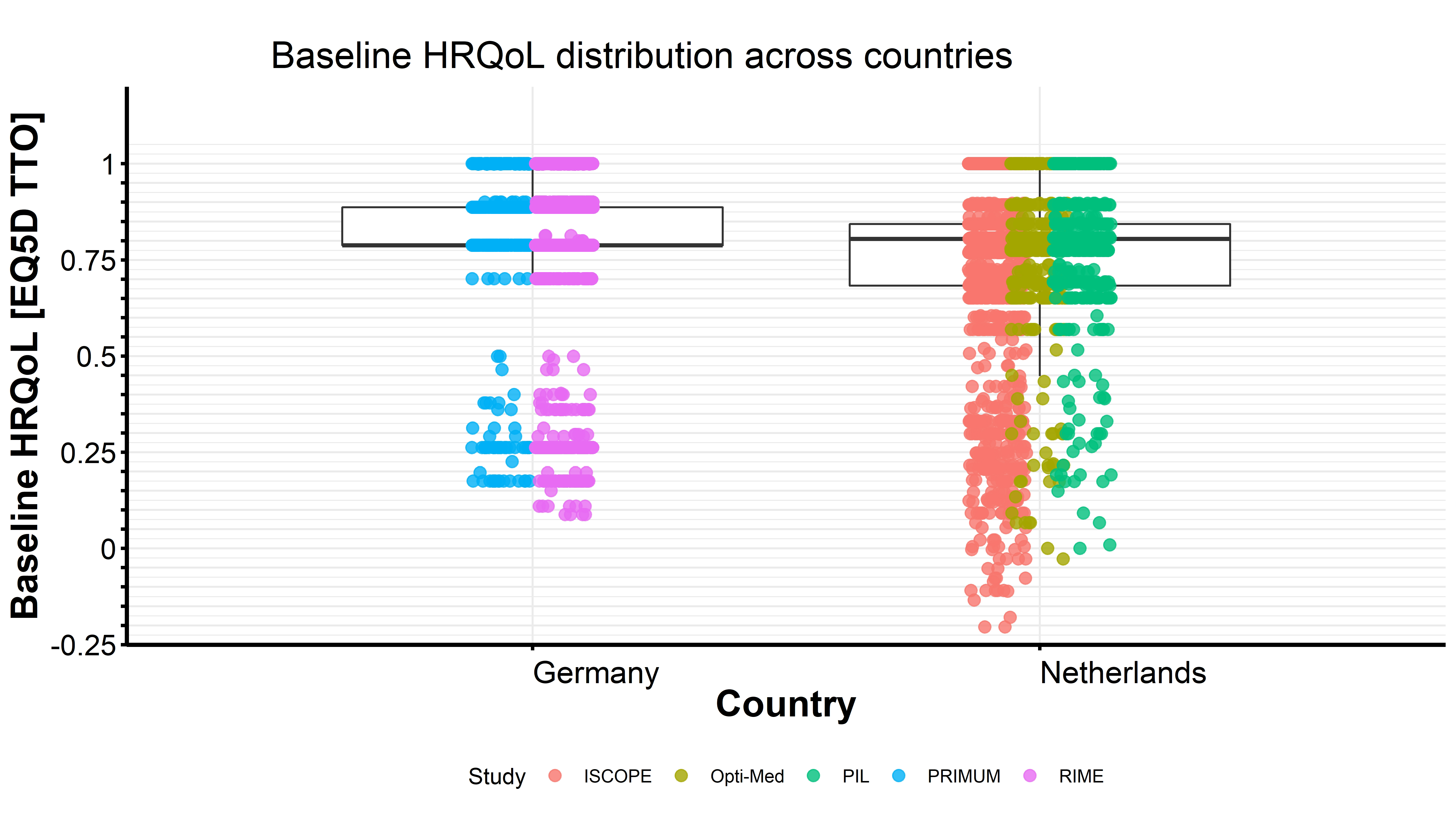
†No. of drugs refer to ATC codes (i.e., single active ingredients or fixed combinations as listed in ATC version 2012).

†† Depression considered possible in case of a positive score on either of the two provided scales (GDS/SF).

a VES-13; b Scale for Mobility problems; c Katz-15; d PRIMUM and ISCOPE GDS 15 (cut-off  5 for categorical variable), RIME GDS 5 (cut-off  2 for categorical variable).

e Opti-Med and RIME MCS score SF-12 (cut-off < 50.2 for categorical variable), and PIL MCS score SF-36 (cut-off < 42 for categorical variable); f von Korff (cut-off  1 for categorical variable); g VAS (cut-off  1 for categorical variable); h PIL SF-36 and RIME SF-12; i single question; j EQ-5D was used in an experimental version in PIL and ISCOPE

**Supplemental figure 1**



**Supplemental figure 2**