Maturitas 97 (2017) 14–20

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Design of a frailty index among community living middle-aged and older people: The Rotterdam study

Josje D. Schoufour[a,*], Nicole S. Erler[a,b], Loes Jaspers[a], Jessica C. Kiefte-de Jong[a,c], Trudy Voortman[a], Gijsbertus Ziere[a], Jan Lindemans[d], Caroline C. Klaver[a,e], Henning Tiemeier[a], Bruno Stricker[a], Arfan M. Ikram[a], Joop S.E. Laven[f], Guy G.O. Brusselle[a,g], Fernando Rivadeneira[a,h], Oscar H. Franco[a]

[a] Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands
[b] Department of Biostatistics, Erasmus MC, Rotterdam, the Netherlands
[c] Leiden University College, The Hague,the Netherlands
[d] Department of Clinical Chemistry, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
[e] Department of Ophthalmology, Erasmus MC, Rotterdam, the Netherlands
[f] Division of Reproductive Medicine, Department of Obstetrics and Gynaecology, Erasmus MC, Rotterdam, the Netherlands
[g] Department of Respiratory Medicine, Erasmus MC, Rotterdam, the Netherlands
[h] Department of Internal Medicine, Erasmus MC, 3000 CA Rotterdam, the Netherlands

ARTICLE INFO

Article history:
Received 7 September 2016
Received in revised form 28 October 2016
Accepted 9 December 2016

Keywords:
Mortality
Frailty index
Missing data
Construct validity
Criterion validity

ABSTRACT

Objectives: To design a frailty index (FI) and evaluate three methods to handle missing data. Furthermore, we evaluated its construct (i.e., skewed distribution, correlation with age and sub-maximum score) and criterion validity (based on mortality risk).
Study design: We included 11,539 participants (45± years) from a population-based cohort in the Netherlands. Frailty was measured with a FI, which we constructed based on the accumulation of 45 health-related variables, related to mood, cognition, functional status, diseases and conditions, biomarkers, and nutritional status. A total FI-score was calculated by averaging the scores of the deficits, resulting in a score between 0 and 1, with higher scores indicating increasing frailty. Mean imputation, single- and multiple imputation were applied.
Main outcome measure: Mortality data were obtained by notification from the municipal administration. Median follow-up time was 9.5 years, during which 3902 (34%) participants died.
Results: The median FI for the full population was 0.16 (IQR = 0.11–0.23). The distribution of the FI was slightly right-skewed, the absolute maximum score was 0.78 and there was a strong correlation with age (Pearson correlation = 0.52;95%CI = 0.51–0.54). The adjusted HR per unit increase in FI-score on mortality was 1.05 (95%CI = 1.05–1.06). Multiple imputation seemed to provide more robust results than mean imputation.
Conclusion: Based on our results we advise to the use of at least 30 deficits from different health domains to construct a FI if data are not imputed. Future research should use the continuous nature of the FI to monitor trajectories in frailty and find preventive strategies.

1. Introduction

In high income countries, life expectancy has more than doubled in recent decades, leading to a tremendous increase in the number of older people [1]. Nevertheless, increased age is often accompanied by decreased health status and reduced quality of life [1]. To limit the burden of ageing and stimulate healthy ageing it is important to understand the ageing process, its contributors and consequences. One commonly used approach to study ageing is via

Abbreviations: FI, frailty index; FI-score, frailty index score; RS, rotterdam study; ROC, receiver operating curve; AUC, area under the curve.

* Corresponding author at: Erasmus MC, Department of Epidemiology, P.O. Box 2040, 300 CA, Rotterdam, The Netherlands.
E-mail addresses: j.schoufour@erasmusmc.nl, josje.schoufour@hotmail.com (J.D. Schoufour).

http://dx.doi.org/10.1016/j.maturitas.2016.12.002
0378-5122/

the concept of frailty, defined as a state of vulnerability to adverse health outcomes at old age [2].

There is no standard approach to conceptualize and measure frailty [3]. Several approaches have been used such as the frailty index (FI) [2], based on the accumulation of health deficits, which can include an unspecified number of symptoms, signs, diseases, disabilities, or laboratory measures as long as they are health and age related [4]. The severity of frailty is represented by the number of deficits and is expressed on a continuous FI-score, calculated as the ratio of the deficits present to the total number of variables considered. By design, the FI allows for a cumulative number of small health issues to contribute to frailty [5]. Because the FI includes deficits from all health domains it can be interpreted as a measure for overall health and has been used as a proxy for biological age [6].

The FI has been applied to a wide range of populations, including hospitalized people, older people with cognitive disabilities, population-based and community-living older people [4,6–10] and populations from different countries and continents [11]. Although the content of these frailty indices differed, they exhibited similar characteristics: distribution skewed to the right, sub-maximum limit, association with age, and prediction of negative health outcomes (e.g. mortality, hospitalization and diseases) [4,6,11,12]. Although most studies provide detailed information on the characteristics and the content (e.g. which deficits they included) of the frailty index they often do not discuss or address the method used to deal with their missing data. In comprehensive datasets missing data are very common and numerous methods exists to deal with these missings when constructing a FI. Nevertheless, the effect that these methods have on the characteristics of the FI are not yet shown. Therefore we aim to design a FI in 11,539 participants within the population-based Rotterdam study and evaluate three methods to handle missing data: (1) ignoring the missing values, (2) single imputation and (3) multiple imputation. Furthermore, we aimed to evaluate the construct and criterion validity of the FI by evaluating the typical characteristics of a FI (i.e., whether it had a skewed distribution, correlated with age and had a sub-maximum score) and the relation of the FI with all-cause mortality

2. Methods

2.1. Study setting

Data from three cohorts of the Rotterdam Study (RS), a prospective population-based cohort, were employed for these analyses. A more detailed description of the RS is provided elsewhere [13]. Briefly, the first baseline visits took place between 1990 and 1993. All residents aged 55 years and over in the Ommoord district of Rotterdam (n = 10,215), the Netherlands, were invited to participate, of which 7983 (78%) took part in the RS's first cohort (RS-I). The study was extended in the year 2000 (RS-II; n = 3011) and in 2006 (RS-III; n = 3932). In total, 14,926 participants were included in the RS, who visited the research center for detailed measurements every 3–4 years. The RS has been approved by the medical ethics committee according to the Wet Bevolkingsonderzoek ERGO (Population Study Act Rotterdam Study), executed by the Ministry of Health, Welfare and Sport of the Netherlands, and written informed consent was obtained from all study participants. For the current analysis we included participants from the third visit of the first cohort (RS-I-3; n = 4785), the first visit of the second cohort (RS-II-1; n = 3011) and the first visit of the third cohort (RS-III-1; n = 3932), comprising 11,728 participants. Eventually, 11,539 participants had sufficient information to be included in the current study.

2.2. Data collection

At baseline, participants were interviewed at home and subsequently visited the research center for a comprehensive set of examinations. The home interview included an extensive set of questionnaires including activities of daily living (ADL; assessed with the Stanford Health Assessment Questionnaire [14]), instrumental activities of daily living (IADL; assessed with the Lawton Instrumental Activities of Daily Living scale [15]), depression (CES-D scale [16]), history of fractures, physical activity, socio-economic status, smoking status and medical history. The examination at the research center included body imaging (i.e. of heart, blood vessels and brain), anthropometric measurements (i.e. body mass index, waist circumference), body composition (whole-body and regional DXA), physical functioning (i.e. grip strength, walking speed) and collection of blood to assess several biomarkers (i.e. homocysteine, hormone levels, vitamin D, cholesterol, CRP).

2.3. Construction of the frailty index

Using a stepwise procedure, variables were evaluated as potential deficits and were included if they satisfied all of the following pre-defined criteria [4]: (1) the deficit is associated with health, (2) the deficit's prevalence or severity generally increases with age, (3) the deficit is not too exceptional (e.g. rare diseases with a prevalence <5%) or too common (e.g. a prevalence above 80%). Full questionnaires or variables were clustered into subcategories or single deficits if required. If items referred to the same topic, their correlation was evaluated and if high ($r > 0.7$) only the one with the highest correlation with age was included. Forty-five variables were selected for the FI. These were deficits related to mood (n = 4), cognition (n = 6), functional status (n = 13), diseases and conditions (n = 11), biomarkers (n = 7) and nutritional status (n = 4). The final list of included deficits and established cut-points is provided in Appendix I in supplementary material. All included deficits were scored such that 1 = deficit present and 0 = deficit absent, intermediate scores were also possible for variables with more categories (i.e. severe vitamin deficiency = 1, mild deficiency = 0.5). A total FI score was calculated by the sum of all deficits divided by the total number of deficits considered resulting in a score ranging theoretically from 0 to 1. For example if a person had 10 out of 45 deficit present his FI score would be 10/45 = 0.22. As such, a larger number of present deficits resulted in a higher score. Not all participants had complete data on all variables available. In order to obtain a stable FI, it has been suggested to use at least 20–30 deficits [4]. Therefore, participants were only included if data on at least 20 deficits were available (n = 11,539).

2.4. Mortality data

All-cause mortality data were obtained by notification from the municipal administration. Data on all-cause mortality and living status were updated until October 2015. Participants were followed from the first day they entered the study till the day of death, the day of lost to follow-up or the last date of contact, whichever came first. The median follow-up for the analysis was 9.5 years (range 0–17.9 years).

2.5. Missing data methods

There are different methods known to handle missing data in a FI. To investigate the impact that different methods of handling missing values in the FI deficits may have, we used and compared three different approaches: 1) ignore missing values, i.e., take the mean over the observed FI variables only, which we will refer to as 'mean imputation', which can be interpreted as replacing them