Quality of Life Research (2019) 28:3047–3054
https://doi.org/10.1007/s11136-019-02243-4

Impact of comorbidities and functional impairment on 5-year loss of health utility in patients with lower-limb osteoarthritis in the KHOALA cohort

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Accepted: 29 June 2019 / Published online: 4 July 2019

Abstract

Purpose To examine the respective and combined impact of "hypothetical" functional impairment (FI) and burden of comorbidities accrual on a 5-year risk of health utility (HU) loss in osteoarthritis (OA).

Methods Participants of the Knee and Hip Osteoarthritis Long-term Assessment (KHOALA) study with a 5-year follow-up were included. FI, number of comorbidities and HU were measured annually by the WOMAC, Functional Comorbidity Index and Short-Form 6D, respectively. We estimated the population risk of HU loss (PRD: population risk difference, PRR: population risk ratio) under hypothetical FI and comorbidities using the parametric G-formula. Then, mediation analysis investigated the causal mechanism of comorbidities on HU through FI by estimating total, direct and indirect effects.

Results We examined data from 767 patients (68.8% women; 61.6 years). The estimated 5-year risk of HU loss was 47.5% [41.9; 52.2] under natural course and 24.9% [15.5; 34.2] when imposing "*Patient acceptable function and No comorbidity*" corresponding to a PRD = − 22.6 [− 26.5; − 21.2] and a PRR = 0.5 [0.4; 0.6]. The estimated total risk of HU loss comparing "*Two comorbidities*" versus "*No comorbidity*" was significant without mediation effect of FI: Total = 10.1% [6.8; 12.9]; direct = 8.0% [2.7; 13.1]; indirect = 2.1% [− 2.0; 5.2].

Conclusions FI and comorbidities are important and independent determinants of HU loss in patient with OA. Half of cases (50%) of HU loss during 5 years could be avoided by preventing comorbidities (30%) and limiting FI under patient acceptable function (20%). Caregivers should additionally pay close attention to the prevention and the treatment of comorbidities in routine management of OA.

Keywords Functional impairment · Comorbidities · Health utility · Lower-limb osteoarthritis

Introduction

Osteoarthritis (OA) is a chronic and frequent joint degenerative disease characterized by a gradual damage of one or multiple joints with several undesirable health consequences [1] such as functional limitation, pain, stiffness, fatigue and limitations in daily living activities. Among the most commonly affected joints are hip and knee [2]. OA increases with ageing and obesity and shares several risk factors with cardiovascular diseases, so people with OA are more likely to develop comorbidities than the general population. Comorbidities are defined as "any distinct additional entity that has existed or may occur during the clinical course of patient who has the index disease under study" [3].

The prevalence of OA is high and is increasing due to the ageing of the population and the obesity epidemic with

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a high cost burden [4–6]. In a context of limited resources, OA is an important public health issue that needs to integrate societal and patient viewpoints for resource allocation which is called health utility (HU). The concept of HU was developed by economists for cost-utility analyses undertaken to inform decision making regarding the efficiency of health care by reflecting societal and patient views. It is expressed as the "desirability or preference that individuals exhibit for the condition" [7]. HU is valued on a scale in which the value of the best imaginable health is 1 and the value of being dead must be 0.

Consequences of OA such as functional impairment (FI) as well as associated comorbidities may impact the HU in patients with OA. Few studies have investigated the association of comorbidities and HU in patients with OA [8]. In a cross-sectional analysis, Hosseini et al. [8] showed that the number of comorbidities, and in particular psychiatric and degenerative back pain, was associated with low HU in OA patients. As well, severity of FI had a greater negative effect on HU than did comorbidities. These findings raised not only the question of the causal relationship between comorbidities, FI and HU in patients with OA but also the mediation effect of FI related to OA in the relationship between comorbidities and HU. However, no randomized trial can specifically be carried out to investigate the causal effect of FI and comorbidities on HU evolution. Moreover, prospective observational studies conducted with classical methods are not adapted to address this issue due to potential time-varying exposure and confounders. A valid estimation of long-term effect of FI and comorbidities on HU requires appropriate statistical methods taking into account time-varying exposure and confounders, as do the parametric G-formula [9]. We applied the parametric G-formula to data from the observational cohort of patients with OA to estimate causal association of comorbidities and FI with the 5-year risk of HU loss and then we conducted a mediation analysis to investigate the causal mechanism of comorbidities on HU through FI. Ours hypotheses were that FI and comorbidities are important determinants of HU loss and the relationship between comorbidities and HU may be partly mediated by the severity of the FI.

Methods

Study sample

This study used data from the Knee and Hip Osteoarthritis Long-term Assessment (KHOALA) cohort study in France. The KHOALA cohort is an ongoing national population-based study of prevalent cases of men and women with uni- or bilateral symptomatic hip and/or knee OA with annual waves of data collection [10]. Participants 40 to 75 years old at baseline were recruited from a prevalence survey in six regions of France between April 2007 and March 2009. They were followed annually with a clinical visit or by mailed self-reporting questionnaire [10]. From the 878 included patients, we excluded those without available data on HU at baseline and year 5 ($n=69$) and patients deceased during follow-up ($n=42$). A total of 767 patients were included in this analysis. The study received ethics committee approval (CIL no. R2016-47) and is registered at www.clinicaltrials.gov (no. NCT02879890).

Measurements

Health utility

Indirect SF-6D HU was computed using the collected data on the SF-36 questionnaire. The SF-6D questionnaire [11] is composed of six dimensions: physical functioning, role limitation, social functioning, pain, mental health and vitality, with 4 or 6 levels in each dimension [12]. A HU scoring algorithm was developed by the standard gamble method from a representative sample of the population in the United Kingdom for scores ranging from 0.29 to 1.00, with 1.00 representing full health and 0.29 representing the worst possible health state defined by the SF-6D (i.e. all domains being at the worst level) [13].

Functional impairment and comorbidities

FI was measured by the French validated version of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [14, 15], with scores for pain, stiffness, function and global dimension. The score for each dimension ranges from 0 (low impairment) to 100 (high impairment). The WOMAC describe limitations in activities due to OA with high scores reflecting increased limitations in activities. Comorbidities were assessed by the Functional Comorbidity Index (FCI) [16], which was specifically developed to assess the impact of comorbidities on the physical dimension of quality of life. This index is composed of 18 conditions (including OA) and allows for calculating the number of comorbidities. In this study, the number of comorbidities was calculated excluding OA.

Data on sociodemographic characteristics (age, sex, weight, height, education level, occupation) and inclusion joint (hip, knee or hip and knee) were collected at baseline. At each follow-up, clinical and HU data were collected.

Hypothetical exposures

Patient acceptable functional impairment was defined as WOMAC score lower or equal to patient acceptable symptom state (PASS) for functional impairment in patients with

hip and knee OA. The PASS is defined as the value bellow which patients consider themselves well [17]. For functional impairment the PASS was 31 and 34 for knee and hip OA, respectively [18]. In this study, we consider patients with WOMAC score ≤ 30 (for all dimensions) of WOMAC as patients with acceptable symptomatic state. We considered 7 hypothetical exposures and their combination using the WOMAC score and the number of comorbidities: patients with "*No comorbidity, FCI = 0 only*" (*exposure 1*), patients in a "Patient a*cceptable symptom state, score ≤ 30*" for each WOMAC dimension: function only (*exposures 2)*, pain only (*exposures 3)*, stiffness only (*exposures 4)* and global only (*exposures 5*), patient in a "*Patient acceptable symptom state, (*WOMAC scores for function, pain, stiffness and global dimensions were ≤ 30*)*" for all of them (*exposure 6*) and patient with "*No comorbidity (FCI = 0) and in patient acceptable symptom state (*WOMAC scores for function, pain, stiffness and global dimensions were ≤ 30*)*" for all WOMAC scores (*exposure 7*).

Statistical analysis

The study outcome was the 5-year HU loss defined as the HU decrease between 0 and 5 year (T5–T0 < 0). We used the parametric G-formula to estimate the 5-year risk of HU loss under hypothetical exposures [19]. The use of the g-formula was motivated by hypothesized time-varying confounding (Fig. 1) and by the desire to estimate the reduction in HU loss from an intervention that could, for example, limited FI < PASS versus FI > PASS. The parametric G-formula is a generalization of standardization for time-varying exposure and outcomes (Fig. 1). The G-formula is an estimating process starting by fitting regression models for all potential confounders and for the outcome using the entire study population and using these models to simulate the risk of the outcome under various level of exposure. This study included fixed-time baseline (sex, age, marital status, professional category, professional status, education level, income level, healthcare coverage, inclusion joint, bilateral OA, hip or knee replacement, inclusion HU score) and time-varying (FCI and the dimensions of FI score) covariates. The steps of the G-formula process are:

Step 1 (Parametric estimation)

We fit regression models for each time-varying covariate at each time *t* as a function of *t* and past *t-1* covariate history (*Step 1a,* linear regression) and for the risk of HU loss by the end of follow-up (year 5) conditional on past covariate history (*Step 1b,* logistic regression).

Step 2 (Monte Carlo simulation)

The Monte Carlo approach was used to generate a large number (simulated sample size of 10,000 patients) of covariates histories consistent with the exposure. Recursively, for each covariate history simulated at *t-1*, value of all covariates at time *t* > *0* were generated using the estimated model coefficients obtained in *Step 1a* (with *t* = 0 covariate values set to the observed data values). After the values of all covariates were generated at time *t*, value of covariates that were to undergo hypothetical exposure were then changed according to the specified exposure rule. This process continued through time *t* = 5. The outcome value was then generated for each of the 10,000 generated histories based on the estimated model coefficient from *Step 1b*.

Step 3 Calculation of risk under each exposure

The final estimate of the population risk under the time-varying specific exposure was the 10,000 history specific outcome risk computed from *Step 2*. *Step 2 and 3* was repeated for each exposure scenario. The bootstrap method was used to estimate the standard errors as well as the confidence intervals of the relative risks estimated in the hypothetical exposures. For this later estimation, we used 20 resamples of size 10,000.

For each model, we estimated the risk of HU loss associated with a respective hypothetical exposure. We set the risk under no hypothetical exposure (natural course) as the reference category, and we estimated the population risk

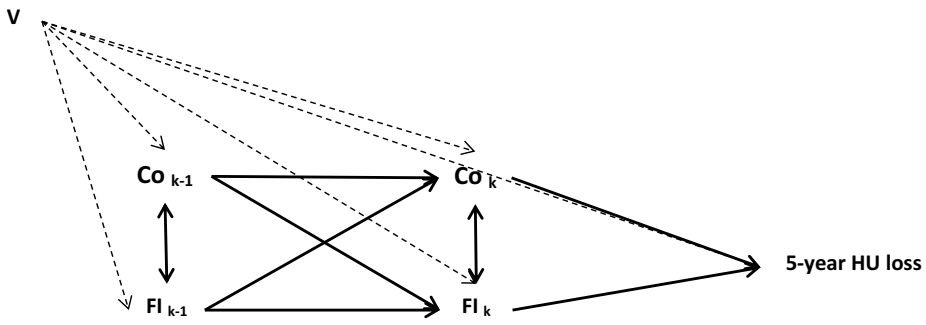

Fig. 1 Directed acyclic graph showing hypothesized causal relationships among study fixed (V) and time-varying (C and FI) variables for years K-1 and K. *Co* comorbidities, *FI* functional impairment, *V* fixed covariates, *HU* health utility

ratio (PRR) and risk difference (PRD) for each exposure scenario. When calculating estimates under natural course, no change was made to any of the value of covariates after they were simulated at time t in *step 2*. Large differences between the observed mean outcome and covariates and the natural course means may suggest poor model fit.

For mediation analysis with time-varying exposure, mediator and confounders, the process was an adapted version of the standard G-formula and involved specifying parametric regression models for the distribution for time-varying exposure (comorbidities), mediator (FI), confounders and outcome (HU loss). The method decomposes the total effect (TE) into exposure (or interventional) direct effect (IDE) and indirect (IIE) effects [20].

We estimated the effect of having two comorbidities (compared with no comorbidity) on the risk of 5-year loss in health utility mediated by global score of the WOMAC. Analyses of HU loss were done using the GFORMULA macro implemented by Taubman et al. [19]. Mediation analyses were done using the mGFORMULA macro implemented by Lin et al. [20]. All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), and the implemented macros (GFORMULA and mGFORMULA) are available at http://www.hsph.harvard.edu/causal/software.

Results

Baseline characteristics of the study sample are presented in Table 1. The mean age of the study sample was 61.6 (8.5) years and it was mostly composed of female (68.8%), married (68.5%) and retired persons (59.2%). Among them, 24.3% and 39.6% had high education level and high monthly income level, respectively. The most frequent damaged joint was knee (69.6%) while only 5.3% had combined knee and hip OA. Baseline mean HU score, number of comorbidities and global score of WOMAC were 0.66 (0.11), 2.0 (1.5) and 33.8 (20.2), respectively.

Table 2 shows the 5-year risk of HU loss under various scenarios of FCI and FI (hypothetical exposure). Under natural course, the 5-year risk of HU loss was 47.5% [95% CI 41.9%, 56.2%] which was close to the observed risk of 5-year HU loss (48.6%). Compared to natural course, the risk of HU loss was low for "*No comorbidities*" (−15.2% [−21.1%, −8.7%]), "*Patient acceptable global score of FI*" (−19.1% [−36.4%, −12.1%]), "*Patient acceptable symptom state (WOMAC pain, function, stiffness and global dimensions)*" (−12.0% [−15.4%, −9.2%]) and "*Patient acceptable symptom state (4 dimension of WOMAC) and no comorbidities*" (−22.6% [−26.5%, −21.2%]) scenarios. We estimated that the 5-year risk of HU loss would be reduced by 30% under "*No comorbidities*" scenario (PRR = 0.7 [0.5, 0.8]),

Table 1 Baseline characteristics of the study sample

	No	%
Sex (women)	528	68.8
Age at inclusion, mean (SD)	767	61.6 (8.5)
Marital status		
Divorced, widowed	198	25.9
Single	43	5.6
Married	523	68.5
Social and professional category		
Unemployed	67	9.6
Employees, manual workers	266	38.1
Farmers, craftsmen, business men	97	13.9
Intermediate profession	157	22.5
Executives, managerial staff	111	15.9
Professional status		
Sick leave, disability, long-term illness	34	4.4
Housewife, houseman	75	9.8
Retired	454	59.2
Active worker (part-time or full-time)	204	26.6
Education level		
Primary/middle school	340	44.5
High school	238	31.2
> High school	185	24.3
Monthly income level		
Low (< 1220 €)	155	21.4
Moderate (1220–2440 €)	282	39.0
High (> 2440 €)	287	39.6
Healthcare coverage		
Social coverage only	35	4.6
Social coverage and supplementary health insurance	713	95.3
Hip or knee replacement (yes)	125	16.3
Joint at inclusion		
Hip	192	25.0
Knee	534	69.6
Hip and knee	41	5.3
Laterality of osteoarthritis		
Unilateral	454	59.2
Bilateral	313	40.8
Baseline health utility score, mean (SD)	767	0.66 (0.11)
Functional impairment (WOMAC)		
Function score	762	33.3 (21.7)
Pain score	766	32.3 (19.2)
Stiffness score	765	41.2 (22.1)
Global score	761	33.8 (20.2)
Comorbidities (FCI)	767	2.0 (1.5)

Data are No and % unless indicated

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, *FCI* Functional Comorbidity Index

Table 2 5-year risks of health utility loss under various exposures of burden of comorbidities and functional impairment

No.	Exposures[c]	5-year HU loss	Population risk ratio (PRR)[a]	Population risk difference (PRD)[a]
		% [95% CI]	Ratio [95% CI]	% [95% CI]
0	Natural course[b]	47.5 [41.9; 56.2]	1.0	0.0
Absence of comorbidity				
1	No comorbidity (FCI = 0 only)	32.3 [21.6; 49.9]	0.7 [0.5; 0.8]	− 15.2 [− 21.1; − 8.7]
Patient acceptable function (FI score ≤ 30)				
2	WOMAC function dimension ≤ 30 only	80.6 [36.0; 87.3]	1.7 [0.8; 1.9]	33.1 [− 7.2; 39.4]
3	WOMAC pain dimension ≤ 30 only	57.6 [38.4; 82.8]	1.2 [0.8; 1.6]	10.1 [− 8.5; 28.5]
4	WOMAC stiffness dimension ≤ 30 only	50.4 [35.2; 70.4]	1.1 [0.8; 1.3]	3.0 [− 8.2; 16.8]
5	WOMAC global dimension ≤ 30 only	28.4 [10.4; 37.0]	0.6 [0.2; 0.8]	− 19.1 [-36.4; − 12.1]
6	All WOMAC dimensions ≤ 30 (function, pain, stiffness and global)	35.5 [28.6; 47.0]	0.8 [0.7; 0.8]	− 12.0 [− 15.4; − 9.2]
Absence of comorbidity and patient acceptable function				
7	Patient acceptable function (All WOMAC dimensions ≤ 30) and no comorbidity (FCI = 0)	24.9 [15.5; 34.2]	0.5 [0.4; 0.6]	− 22.6 [− 26.5; − 21.2]

FI functional impairment, *HU* health utility, *95% CI* 95% confidence interval. The observed risk was 48.6%

[a]All models included lagged values of time-varying covariates (function, pain, stiffness and global scores, comorbidities) plus baseline non-time-varying variables: sex, age, marital status, professional category, professional status, education level, income level, healthcare coverage, inclusion joint, bilateral OA, hip or knee replacement, inclusion HU score

[b]Reference category

[c]Simulated exposure under parametric G-formula modelling based on observed data

Table 3 Estimates of the overall effect of 2 comorbidities (compared with no comorbidity) on risk of 5-year health utility loss

Exposure[a]	5-year decrease in HU score	Population risk ratio (PRR)[b]		Population risk difference (PRD)[b]	
	%	%	95% CI		95% CI
No comorbidity[c]	32.5	1.0	–	0.0	–
Two comorbidities	43.4	1.3	1.1; 1.6	10.9	7.3; 14.2

HU health utility, *95% CI* 95% confidence interval. The observed risk was 48.6%

[a]Simulated exposure under parametric G-formula modelling based on observed data

[b]All models included lagged values of time-varying covariates (function, pain, stiffness and global scores, comorbidities) plus baseline non-time-varying variables: sex, age, marital status, professional category, professional status, education level, income level, healthcare coverage, inclusion joint, bilateral OA, hip or knee replacement, inclusion HU score

[c]Reference category

by 20% under "*Patient acceptable symptom state*" scenario (PRR = 0.8 [0.7, 0.8]) and by 50% under the combined two scenarios (PRR = 0.5 [0.4, 0.6]).

Table 4 Estimates of the effect of 2 comorbidities (compared with no comorbidity) on risk of 5-year decrease in health utility mediated by functional impairment score

	Estimate (%)	95% CI
Total effect	10.1	6.8; 12.9
Direct effect	8.0	2.7; 13.1
Indirect effect	2.1	− 2.0; 5.2
Proportion mediated	21.5	− 29.0; 66.0

95% CI 95% confidence interval

For mediation analysis, the estimated 5-year risk of HU loss under "*No comorbidities*" and "*Two comorbidities*" were 32.5% and 43.4%, respectively (Table 3). Compared to "No comorbidity", accruing two comorbidities during the 5 years follow-up increased the risk of HU loss by 10.1% [6.8; 12.9], with an estimated direct effect of 8% [2.7; 13.1] and estimated indirect effect of 2.1% [− 2.0; 5.2] through time-varying global score of FI pathways (Table 4).

Discussion

The results of this study suggest that, in a representative population-based cohort of patients with hip and knee OA, 50% of cases of HU loss could have been prevented by a combination of limiting FI to a patient acceptable function and avoiding comorbidities. Comorbidities and FI had an impact on the risk of 5-year HU loss but this impact seemed to be independent. No-mediating effect of FI on the relationship between comorbidities and HU loss was demonstrated.

In many Western countries, economic evaluations are a prerequisite for health insurance reimbursement for treatments for chronic conditions because they can provide healthcare decision makers with valuable information on the relative efficiency of health technologies or treatments. The HU score for health states experienced by patients can be combined with the length of time spent in these states to produce a total number of quality-adjusted life-years (QALYs) over the time frame of the comparison [21]. QALYs are the most commonly used metric for cost-utility analysis which is the standard approach for assessing the value for money spent on health technologies or treatments. Indeed, demonstration of value for money is commonly required by insurers considering coverage of new health technologies.

The findings of this study show that the burden of comorbidities as well as of FI is important determinants of HU in patients with knee and hip OA. The burden of comorbidities has been shown to be an important risk factor of 5-year HU loss. Similar cross-sectional results were found using inclusion data of the same cohort (KHOALA) [8]. Our findings are similar to those reported on the impact of chronic conditions on health-related quality of life. Major chronic diseases such arthritis, heart disease and diabetes are associated with poor HU and emphasis the need for development of strategies of prevention and control of comorbidities in patient with any chronic disease [22]. Likewise, limiting FI was shown to have positive impact on HU. Remarkably, in this study we found that, with respect to natural course of OA, a limitation of FI under patient acceptable function was associated with a 20% lower risk of HU loss. These results suggested that treatment with positive effect on FI could be cost-effective.

The risk of HU loss was higher if all dimensions of the WOMAC are acceptable than if only the global dimension is acceptable which can be surprising. This result was due to the fact that patients with acceptable pain, function and stiffness seemed to have higher risk of HU loss (even if it was not statistically different from the natural course) than those with only acceptable global score. The possible explanation is that there were almost as many patients with good as with those with bad score especially for function score (mean score of WOMAC close to 30 at each follow-up) resulting in a weak predictive effect of the function dimension. Function score was not discriminating enough to predict HU loss. Using global score to evaluate FI may be more relevant than other dimensions.

Although comorbidities and FI were found to be important predictors of 5-year HU loss, no mediation effect was found between them. The assumption that the effect of comorbidities on the risk of 5-year HU loss could be mediated by the level of FI could not be confirmed. This finding reflects the fact that comorbidities should be more systematically taken into account by caregivers. Mediation analysis involves specifying the hypothetic baseline level of exposure (comorbidities) and the hypothetic new exposure level. In this study we have chosen "No comorbidity" as baseline exposure level and "Two comorbidities" as new exposure scenario because patients of the KHOALA cohort had a mean number of two comorbidities at inclusion.

Our study has some limitations. First, our estimates may not be generalizable to other populations with different distribution of FI and comorbidities, as the G-formula standardizes the risk of HU loss to the distribution of FI and comorbidities in the particular population under study. This situation may be problematic if the study sample was not representative of the population of OA in France. However, the KHOALA cohort is a large and representative sample of cases of OA in the French general population with a relative long-term follow-up (5 years), which enables the generalization of the results.

Second, HU was measured indirectly with a self-reported questionnaire, which could imply measurement bias. However, the SF-6D is a valid questionnaire developed using standard and accurate methods in a UK large sample and is commonly used to measure HU [12, 13]. This study has also some strength. It was the first to investigate the causal relationship between FI, comorbidities and HU in patients with knee and hip OA using longitudinal data and methods suited to causality inference with observational data. The predicted model using the parametric G-formula was robust because simulated data were similar to observed one (generated risk of HU loss under natural course was close to observed risk. Among methods for longitudinal data analysis, the G-formula approach was chosen because of appropriateness to adjust for time-varying confounders that are affected by prior exposure; and for identification of an outcome distribution under a user-specified intervention (or exposure) if the study population had that intervention (or exposure) been implemented, possibly contrary to fact, in all individuals in the population. The results of this study confirmed a major interest on both managing FI related to OA and paying attention to potential comorbidities in clinical practice. However, questions remain about the most effective and cost-effective care strategy that can act simultaneously

on reducing FI and preventing or caring comorbidities, due to the high prevalence of OA with a high cost burden in a context of limited resources.

Conclusion

In summary, our results suggested that FI and comorbidities are important and independent determinants of HU loss in patient with OA. Half of cases (50%) of HU loss during 5 years could be avoided by preventing comorbidities (30%) and limiting FI under patient acceptable function (20%). Caregivers should additionally pay close attention to the prevention and the treatment of comorbidities in their routine management of lower-limb OA.

Acknowledgements Many people worked together selflessly and enthusiastically to make the KHOALA cohort study a success. All the authors of this article warmly acknowledge hospitals and professionals who contributed to the recruitment and follow-up of patients since 2007.

Funding This work was supported by Centre Hospitalier Régional et Universitaire de Nancy (CPRC 2013: R2016-47). Funding for the KHOALA cohort study was obtained from public sources (INSERM, CHU de Nancy, Conseil Régional de Lorraine, Société Française de Rhumatologie) and unrestricted grants from pharmaceutical companies (Expanscience, Genevrier, Grünenthal, Merck & Co, Inc, Pfizer, Pierre Fabre Médicaments, Sanofi-Aventis France). Opinions expressed in the present article are those of the authors and do not necessarily reflect those of the sponsors. The study sponsors did not take part in study design, collection, analysis and interpretation of data, writing of the report or the decision to submit the article for publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study received ethics committee approval (CIL no. R 2016-47).

Informed consent Informed consent was obtained from all individual participants included in the study.

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