European Journal of Radiology 84 (2015) 975–979

Contents lists available at ScienceDirect

European Journal of Radiology

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

Lung structure and function relation in systemic sclerosis: Application of lung densitometry

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ARTICLE INFO

Article history:
Received 28 October 2014
Received in revised form 3 January 2015
Accepted 13 January 2015

Keywords:
Systemic sclerosis
Interstitial lung disease
Lung densitometry
Chest CT imaging

ABSTRACT

Introduction: Interstitial lung disease occurs frequently in patients with systemic sclerosis (SSc). Quantitative computed tomography (CT) densitometry using the percentile density method may provide a sensitive assessment of lung structure for monitoring parenchymal damage. Therefore, we aimed to evaluate the optimal percentile density score in SSc by quantitative CT densitometry, against pulmonary function.

Material and methods: We investigated 41 SSc patients by chest CT scan, spirometry and gas transfer tests. Lung volumes and the *n*th percentile density (between 1 and 99%) of the entire lungs were calculated from CT histograms. The *n*th percentile density is defined as the threshold value of densities expressed in Hounsfield units. A prerequisite for an optimal percentage was its correlation with baseline DLCO %predicted. Two patients showed distinct changes in lung function 2 years after baseline. We obtained CT scans from these patients and performed progression analysis.

Results: Regression analysis for the relation between DLCO %predicted and the *n*th percentile density was optimal at 85% (Perc85). There was significant agreement between Perc85 and DLCO %predicted ($R = -0.49$, $P = 0.001$) and FVC %predicted ($R = -0.64$, $P < 0.001$). Two patients showed a marked change in Perc85 over a 2 year period, but the localization of change differed clearly.

Conclusions: We identified Perc85 as optimal lung density parameter, which correlated significantly with DLCO and FVC, confirming a lung parenchymal structure–function relation in SSc. This provides support for future studies to determine whether structural changes do precede lung function decline.

1. Introduction

Clinical risk assessment of organ manifestations in systemic sclerosis (SSc) has revealed that interstitial lung disease (ILD) is present in 53% of cases with diffuse cutaneous SSc (dcSSC) and in 35% of cases with limited cutaneous SSc (lcSSc) [1]. For evaluating the response to treatment of ILD, pulmonary function tests (PFTs) such as the diffusion capacity for carbon monoxide (DLCO) and forced vital capacity (FVC) are key outcome measures. However, these measures are affected by pulmonary vascular changes and chest wall skin stiffening, respectively [1]. Therefore, more specific measures of lung parenchymal involvement of ILD may provide additional structural information.

Currently, chest high-resolution computed tomography (HRCT) is considered the most accurate noninvasive imaging method for ILD assessment. Both severity and extent of ILD are usually estimated by semi-quantitative scoring of a limited number of cross-sectional slices through the lungs [2,3]. However, visual scoring has limited reproducibility, because of its subjective nature, and is time-consuming, thereby constraining the number of slices that can be assessed. HRCT data provide a means to quantitatively analyze the structure of the whole lung, since inflammation, ground glass opacities and fibrosis can be quantified by lung densitometry. Therefore, objective quantitative techniques by CT densitometry

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http://dx.doi.org/10.1016/j.ejrad.2015.01.012
0720-048X/

may provide a more sensitive measurement, similar to what has been proven in assessing progression of pulmonary emphysema by the percentile density method [4]. Since these quantitative techniques are automated, it is feasible to quantify the entire lungs instead of only a limited number of slices, with a smaller chance of missing pathological changes.

Previously, Camiciotolli et al. [5] reported that lung density histogram parameters are more reproducible than visual assessment of HRCT and are more closely related to functional, exercise and quality-of-life impairment in SSc. In their evaluation of each patient, they calculated the average global density of the lung and included kurtosis and skewness of the density histogram of the whole lung. However, this analysis did not provide a single overall score for the structure of the lungs and, more importantly, lung density values were not corrected for lung volume. In a recent report, the same investigators clearly demonstrated the need for volume correction of density parameters [6]. By a so-called sponge model [7], in which the lungs are considered mass preserving (i.e. the total lung mass is constant during breathing), density values can be corrected in a relatively simple calculation. Volume-corrected lung density parameters calculated by specific software may be useful outcome measures in evaluating the progression of ILD and the response to treatment. Therefore, the aim of this study was to identify the optimal volume correction and percentage threshold for the percentile density method in SSc.

2. Material and methods

2.1. Patients

We investigated 41 patients with SSc who were referred consecutively to our tertiary outpatient targeted multidisciplinary healthcare program. As part of this program, all patients underwent, among other tests, PFTs and an HRCT scan of the thorax; they were instructed to take their usual medication before scanning. Included patients were classified as lcSSc or dcSSc according to LeRoy et al. [8]. The local Medical Ethical Committee approved the protocol. Written informed consent was obtained from each patient prior to enrolment. In two individual patients PFTs (both FVC and DLCO) significantly changed during clinical follow-up. To analyze this we performed additional CT scans.

2.2. Pulmonary function testing

All SSc patients had lung volume, spirometry and gas transfer studies. These PFTs included inspiratory vital capacity, total lung capacity, FVC, forced expiratory volume in 1 s and single-breath DLCO. Results are expressed as a percentage of the predicted value [9,10].

2.3. Computed tomography

All patients were scanned during full inspiration without contrast enhancement by the same CT scanner (Aquilion 64, Toshiba Medical Systems, Otawara, Japan), calibrated according to the manufacturer's guidelines. The standardized protocol comprised the following: tube voltage = 120 kVp; tube current = 140 mA without modulation; rotation time = 0.4 s; collimation = 64 × 0.5 mm; helical beam pitch = 0.8. Axial slices were reconstructed for visual ILD scoring with 0.5 mm slices with 0.4 mm increment and lung kernel (FC30), and for densitometry with 5 mm thick slices with an increment of 2.5 mm and smooth kernel (FC03).

2.4. Image analysis

Images were processed by Pulmo-CMS software (version 2.1, Medis medical imaging systems BV, Leiden, the Netherlands) [11]. The CT scans were first recalibrated on the basis of densities measured in extrathoracic air and blood in the descending aorta [12]. After automated lung contour detection with user correction options was complete, lung volumes and the *n*th percentile density of the entire lungs were calculated. The *n*th percentile density is defined as the threshold value of densities expressed in Hounsfield units (HU), below which *n*% of all lung voxels in the CT images are distributed (as schematically illustrated in Fig. 1). In order to optimize the percentile method, we calculated all percentile densities by using percentages between 5% and 95% (Perc5–Perc95) with increments of 5%.

Subclinical parenchymal lung disease was previously defined as high attenuation areas (%HAAs) within the lung fields having a CT attenuation value between −600 and −260 HU [13]. For comparison, we therefore performed a similar analysis in our data set of lung densities. Finally, an experienced chest radiologist (LK) scored all CT scans visually according to the Kazerooni scoring system [3].

2.5. Statistical analysis

Optimization of the percentile density method was based on the correlation between *n*th percentile density and DLCO, which should be as high as possible. This was investigated by regression analysis, with DLCO as the dependent variable and one of the *n*th percentile densities as the independent variable. Lung volume was entered as a covariate to correct for different lung sizes. The partial correlation coefficient was then plotted against the percentage *n*. The statistical analysis was performed by using SPSS version 20.0.2, with a programmability extension for python scripting. The relation between the percentile and the correlation coefficient was automatically plotted by using Matplotlib [14].

Using the optimal percentage for the percentile density method, we investigated the cross-sectional correlations with the remaining lung function parameters. In addition, we studied the correlation of %HAA with the cross-sectional DLCO %predicted and FVC %predicted.

2.6. Progression map analysis

We noticed distinct changes in the FVC %predicted and DLCO %predicted during clinical follow-up of our patient population. Therefore we obtained CT scans from these patients and performed a recently published progression analysis between baseline and follow-up CT scans [15]. Local changes in lung density were computed by progression analysis [15]. Corresponding locations in the CT scans between baseline and follow-up were obtained by non-rigid intensity-based image registration using elastix [16]. After we corrected for lung volume differences with the sponge model, local changes in lung density were calculated and displayed [15].

3. Results

The clinical characteristics of the 41 SSc patients (lcSSc: $n = 15$) in this prospective cross-sectional study are shown in Table 1.

3.1. Determination of the optimal percentage

From the regression analysis (with CT-derived lung volume as a covariate), we found that the relation between the gas transfer

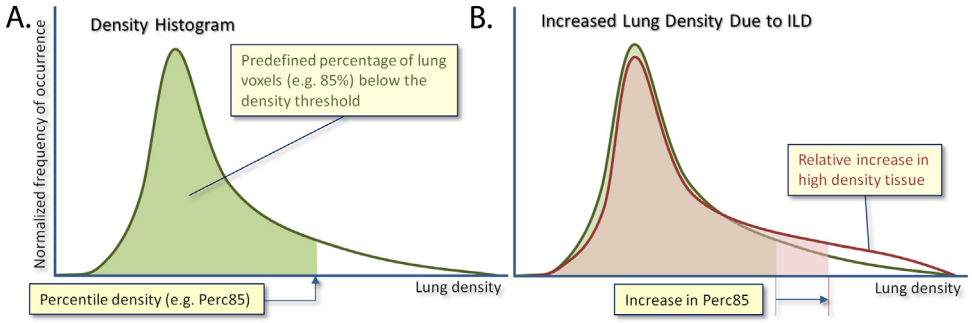

Fig. 1. Schematic graph of the definition of the *n*th percentile density. (A) A normalized histogram of lung densities is shown (i.e., with a total area under the curve of 100%). The percentile density threshold is chosen in such a way that a predefined percentage (e.g., $n = 85$) of all lung voxels (3D pixels) contains densities lower than the threshold, indicated by the green area. (B) Because of interstitial lung disease (ILD), certain lung densities increase, causing the normalized histogram to change shape, where there are relatively more voxels with higher densities (green curve: normal density distribution; red curve: shifted distribution with increased densities). As a result, the percentile density has increased.

factor DLCO (as %predicted) and the *n*th percentile density was optimal at 85% (Perc85), with a partial correlation coefficient of −0.32, as shown in Fig. 2. The slope between Perc85 and DLCO was −0.069 (95% confidence interval: −1.36 to −0.001).

3.2. Relation between structure and function

In the remainder of this report, Perc85 is used as the optimal parameter. There was a moderate agreement between Perc85 and both DLCO %predicted ($R = -0.49$, $P = 0.001$) and FVC %predicted ($R = -0.64$, $P < 0.001$) (Fig. 3A and B, respectively). Kazerooni scores correlated significantly with Perc85 ($R = 0.56$, $P < 0.01$). For the alternative densitometric method by %HAA, Spearman's correlation with DLCO %predicted was $R = -0.48$ ($P = 0.002$) and with FVC %predicted was −0.62 ($P < 0.001$).

Table 1
Clinical data of SSc patients.

	lcSSc	dcSSc
Demographic data and serology		
Number of patients ($n = 41$)	15	26
Age	54.7 (14.5)	48.7 (11.3)
Sex (female)	11 (73)	20 (83)
Disease duration, years	5.8 (7.4)	4.6 (3.5)
Onset of Raynaud, years	12.7 (11.3)	7.1 (4.8)
Caucasian origin (year/*n*)	13 (87)	18 (69)
Modified Rodnan skin score	6 (4–9)	9 (5–15)
Number of patients with		
Antinuclear antibodies	14	21
Anti-centromere antibodies	7	4
Anti-Scl-70	2	16
Overall treatment		
ASCT	0 (0)	9 (22)
Cyclophosphamide	0 (0)	11 (27)
Methotrexate	3 (7)	5 (12)
Rituximab	0 (0)	5 (12)
Mycophenolate-mofetil	1 (2)	4 (10)
Azathioprine	1 (2)	0 (0)
Pulmonary function		
FVC, L	3.34 (0.76)	3.37 (0.99)
FVC, %predicted	104.7 (26.5)	90.7 (19.5)
DLCO, mL/min/mmHg	5.67 (1.23)	6.06 (2.22)
DLCO, %predicted	67.7 (12.4)	64.0 (14.6)
FVC/DLCO	0.67 (0.17)	0.68 (0.19)

Data presented as mean (SD) or as median (25–75th percentile), *n* (%). lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; ASCT: autologous stem cell transplantation; FVC: forced vital capacity; DLCO: single breath diffusion capacity of the lung for carbon monoxide.

3.3. Prospective application in individual study data: progression map analysis

Two isolated individuals in our SSc population showed marked change in their clinical course. After the observed change in their FVC (+24 and +8%pred) and DLCO (+11 and +5%pred), we decided to image their lungs by a similar CT scan. These data were not part of our cross-sectional study. Details of the two patients with diffuse SSc were analyzed extensively by local progression analysis [15]. Fig. 4 shows a local decrease lung density (in HU) in both patients, albeit in different locations in the lung and with different patterns. Both patients had ground glass densities that partly resolved after 1 year, in patient B this returned to the average values of the study population.

4. Discussion

We studied the lung tissue structure by histogram analysis of lung densities obtained from CT images of patients with SSc. We report that the 85th percentile density score (Perc85) represents the most informative density parameter to assess lung parenchyma in SSc. Perc85 significantly correlated with DLCO as a measure of gas transfer. Interestingly, the lower percentile densities showed a positive relation between density and DLCO, indicating that low lung densities in SSc are accompanied by relatively high gas transfer

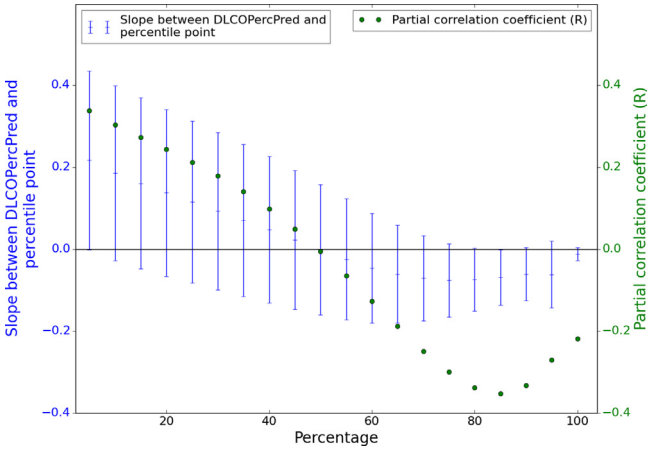

Fig. 2. Partial correlation between percentile density and DLCO %predicted, against the percentage used for defining the percentile density. For each percentage, the slope is plotted with 95% confidence intervals (blue error bars). The corresponding partial correlation coefficient is indicated by green dots. Lung volume during CT scanning was entered in the regression analysis as a covariate.

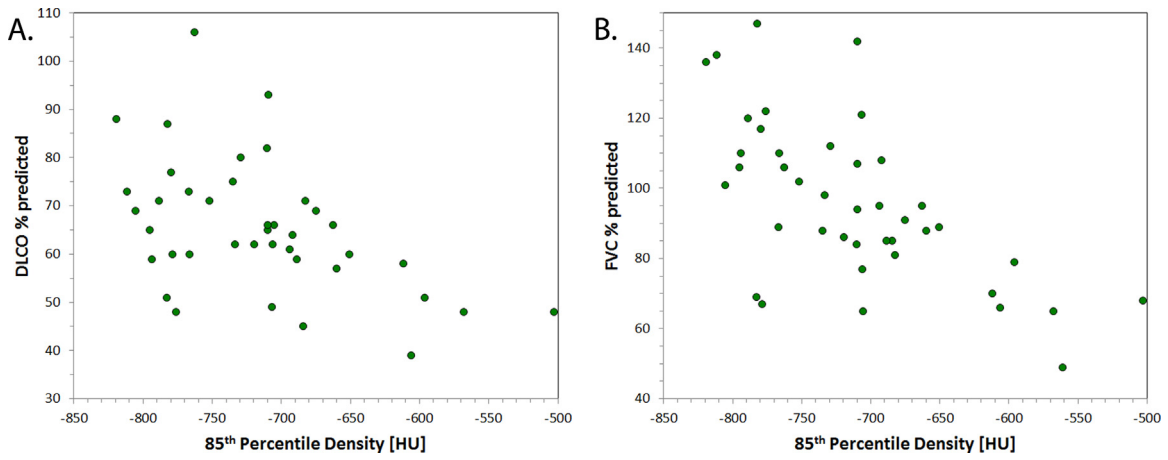

Fig. 3. Correlation between lung structure and function. (A) Correlation between volume-corrected 85th percentile density and CO diffusion capacity ($R = -0.49$, $P = 0.001$). (B) Correlation between volume-corrected 85th percentile density and forced vital capacity ($R = -0.64$, $P < 0.001$).

values. Higher percentile densities showed the opposite, i.e., higher lung densities are associated with a relatively low gas transfer. This suggests that changes in lung density correlate with clinically relevant functional changes in patients with various severities of SSc. Indeed, two cases with marked improvement in FVC and DLCO related to a marked decline in Perc85.

The analysis of lung structure by densitometry of CT images provides a rapid and operator-independent assessment of lung pathology in SSc. Percentile density analysis of the histogram of tissue densities for both lungs is new in the analysis of ILD. The Perc85 point contains all densities present in the histogram between the density of air (−1000 HU) and the Hounsfield unit at which 85% of the densities in the histogram is captured. We considered DLCO rather than FVC as the most appropriate functional parameter for determining the optimal percentile density, although FVC is the most frequently reported outcome parameter in SSc for analysis of ILD [17,18]. By using FVC only for the ultimate evaluation of the optimized parameter, we avoided introducing bias.

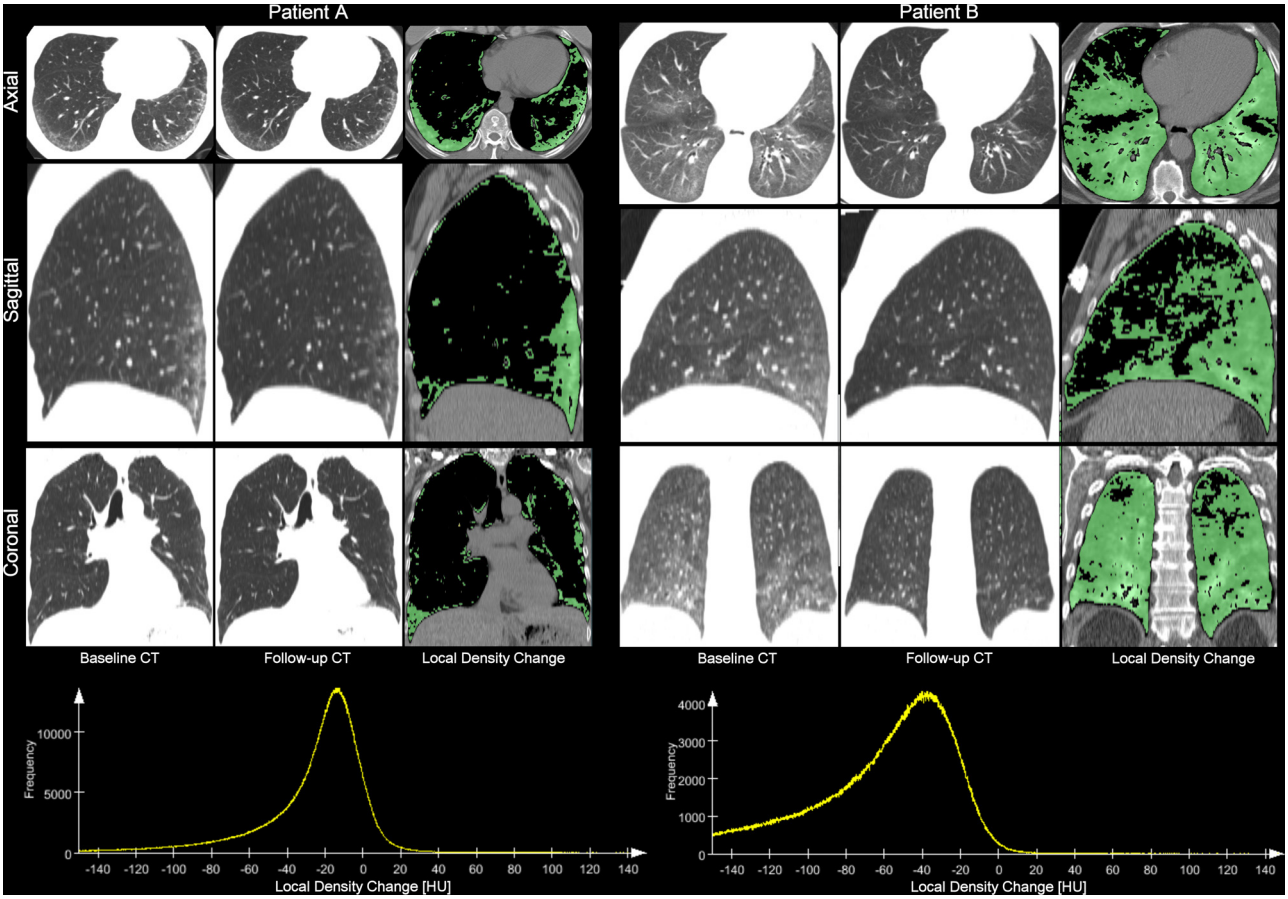

Fig. 4. Local progression analysis for two patients with marked change in their clinical course. For each patient, the axial sagittal and coronal CT images are shown: in the first column, the baseline CT scans are shown; in the second column, the CT scans at follow-up are shown and are elastically transformed to match the baseline scans, by image registration; the third column shows the local difference in density after volume correction. The green areas indicate significant changes in local densities (the brightness of the green overlay corresponds to the size of the density change). At the bottom, the histograms of the local density changes for each voxel are shown, where a positive change indicates a density increase and a negative change a density decrease. Both patients show a clear decrease in densities, but with clearly different local patterns.

Therefore, we calculated the correlation between DLCO %predicted of our SSc patients and all percentiles of the density histogram of each CT scan, which were corrected for lung volume. Again, this resulted in the 85th percentile density as the optimum lung density for analysis of lung structure.

Interestingly, two patients had a substantial change in both FVC and Perc85. By application of recently developed software [15], we demonstrated that areas with a decrease in lung density over time can be identified in the lungs, suggesting an improvement in the quality of lung tissue, and that these were accompanied by an increase in FVC and DLCO. Data from these two patients suggest that small changes in lung density do precede changes in their FVC and DLCO. However, assessment of a larger number of patients and a longer time interval are needed in future studies to confirm this observation and to evaluate the clinical benefit of lung densitometry.

The present study has some limitations. The range of lung function restriction was rather limited. A wider range of lung function restriction is needed to elucidate whether Perc85 will be able to detect changes in lung density over the entire severity spectrum of SSc. Validation of lung density against quantitative pathology scores of SSc-affected lung tissue is almost impossible. Unlike in pulmonary emphysema, no quantitative pathology score is available that can be used in the analysis of lobectomy or pneumonectomy tissue specimens from SSc patients [19]. However, some studies have used qualitative pathology scores on open lung biopsy specimens from ILD patients, and these related significantly to lung HRCT scores [3,20]. Furthermore, we found that one such score, published by Kazerooni [3], correlated significantly with Perc85. The latter may suggest a possible correlation between a pathology score and our Perc85 score for lung tissue structure.

5. Conclusions

We identified an optimal lung density parameter, Perc85, which correlated significantly with gas transfer in the lung and may be used to assess clinically relevant changes in lung structure that coincide with changes in lung function. Future studies are needed to determine whether a change in Perc85 will precede changes in FVC and gas transfer to support clinical decision making on early treatment intervention in SSc patients.

Contribution

Contribution	Authors
Study concepts	MK Ninaber, J Stolk, ME Bakker, BC Stoel
Study design	MK Ninaber, J Stolk, ME Bakker, M Staring, BC Stoel
Data acquisition	MK Ninaber, J Smit, E Le Roy, AA Schouffoer, L Kroft, J de Vries-Bouwstra, ME Bakker
Quality control of data and algorithms	MK Ninaber, J Stolk, ME Bakker, BC Stoel, M Staring
Data analysis and interpretation	MK Ninaber, J Stolk, ME Bakker, BC Stoel, M Staring
Statistical analysis	MK Ninaber, J Stolk, ME Bakker, BC Stoel, M Staring
Manuscript preparation	MK Ninaber, J Stolk, ME Bakker, BC Stoel, M Staring
Manuscript editing	MK Ninaber, J Stolk, J Smit, E Le Roy, L Kroft, AA Schouffoer, J de Vries-Bouwstra, ME Bakker, M Staring, BC Stoel
Manuscript review	MK Ninaber, J Stolk, J Smit, E Le Roy, L Kroft, AA Schouffoer, J de Vries-Bouwstra, ME Bakker, M Staring, BC Stoel

Funding

None.

Conflict of interest

All authors declare no conflict of interest.

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