Title: Patient-reported measures and lifestyle are associated with deterioration in nutritional status in CKD stage 4-5: the EQUAL cohort study

Abstract

Objective: The aim of this study was to explore the changes in nutritional status before dialysis initiation, and to identify modifiable risk factors of nutritional status decline in older adults with advanced renal disease.

Design and methods: The European Quality Study on treatment in advanced chronic kidney disease (EQUAL) is a prospective, observational cohort study involving six European countries. We included 1103 adults >65 years with incident eGFR < 20 ml/min/1.73m² not on dialysis, attending nephrology care. Nutritional status was assessed with the 7 point Subjective Global Assessment tool (7-p SGA), patient-reported outcomes with RAND-36 and the Dialysis Symptom Index. Logistic regression was used to estimate the associations between potential risk factors and SGA decline.

Results: The majority of the patients had a normal nutritional status at baseline, 28% were moderately malnourished (SGA ≤5). Overall, mean SGA decreased by -0.18 points/year, (95% CI -0.21; -0.14). More than one-third of the study participants (34.9%) deteriorated in nutritional status (1 point decline in SGA) and 10.9% had a severe decline in SGA (≥ 2 points). The proportion of patients with low SGA (≤5) increased every six months. Those who dropped in SGA also declined in eGFR and mental health score. Every 10 points decrease in physical function score increased the odds of decline in SGA by 23%. Lower physical function score at baseline, gastrointestinal symptoms and smoking were risk factors for impaired nutritional status. There was an interaction between diabetes and physical function on SGA decline.

Conclusions: Nutritional status deteriorated in more than one-third of the study participants during the first year of follow-up. Lower patient reported physical function, more gastrointestinal symptoms, and current smoking were associated with decline in nutritional status.

Key words: Chronic kidney disease, Nutritional status**,** Patient Reported Outcome Measures, 7-point SGA, RAND-36

Introduction

Older adults with advanced chronic kidney disease (CKD) form a high-risk group for poor nutritional status and high overall disease burden (1, 2). The prevalence of protein-energy wasting (PEW) in this vulnerable population is high, and increases with age (3). Patients who undergo maintenance dialysis have a significant decline in nutritional parameters, and those diagnosed with PEW have a higher risk of mortality and hospitalizations (4, 5). In addition to the normal ageing process, the uremic milieu promote premature ageing processes (6). The aetiology of uremic ageing and PEW has been described (6, 7), but less is known about modifiable determinants that may influence the course of nutritional status. Cognitive and physical decline associates with poor nutritional status in the general geriatric population (8-10). The underlying mechanism is complex, but both the somatic status and mental health are linked to lifestyle, perceived health and frailty in older adults (10).

The organisation and access to renal care varies widely across the world (11). In many countries, advanced CKD care is characterized as an intensified treatment program, aiming to prepare the patient for kidney replacement therapy or conservative care (12-14). However, this crucial phase is not well studied in the elderly CKD population from a nutritional perspective. A first step in this direction is to observe and evaluate factors influencing nutritional status with a holistic approach. The aim of this study is therefore to explore the changes in nutritional status in elderly people with advanced stage CKD, and to investigate if modifiable risk factors such as patient-reported gastrointestinal symptoms, mental health, physical function, and life-style factors were associated with change in nutritional status over time. For this purpose, we used a large European inception cohort of patients aged >65 years with stage 4-5 CKD with repeated measurements of Subjective Global Assessments (SGA).

Methods

Study design and study population

The EQUAL-study is a multicentre, prospective cohort study in six European countries (Germany, Italy, the Netherlands, Poland, Sweden and United Kingdom). Inclusion criteria are older adults (>65 years) with an incident estimated glomerular filtration rate ($eGFR_{mdrd}$) < 20 ml/min/1.73m². The patients were followed every 3-6 months and received routine medical care as provided by the nephrology clinics in each country. Standardized data were collected at each visit, including demographics, lifestyle, comorbidities, uremic signs and symptoms, quality of life (RAND-36) nutritional status assessed by subjective global assessment (SGA), medication and routine blood and urine biochemistry. Patients were followed up to four years. A full description of the study protocol has been published elsewhere (15). For this study, we included participants who had entered the study before May 30, 2017 and had performed a nutritional assessment at baseline and at least once more during the following year (**Figure S1**). For the main analyses, we used data from the first 12 months of follow-up. Additionally, we used data from the entire follow-up, up to four years, to calculate the mean nutritional status decline.

Ethics

All study participants signed a written informed consent and the EQUAL study was approved by the ethical review boards in all participating countries.

Nutritional status

Nutritional status was assessed with the 7-point SGA, which is a validated and well-established method to assess nutritional status in nephrology and in other disciplines (16-18). SGA is composed of four domains; history of weight change, history of dietary intake and

gastrointestinal symptoms, a physical examination with visual inspection to screen for loss of fat mass and muscle wasting. Originally, the subscales and the overall score were classified into 3 groups (18-20). This method was further developed by Visser et al (21) to better fit with repeated measurements. The scale ranges from 1-7, where seven corresponds to a good nutritional status and <3 to severe malnutrition. To ensure good quality and reproducibility, all centers participating in the EQUAL study were offered standardized training of the SGA. We defined a decline in nutritional status as at least 1 point decline in SGA at any visit during the first 12 months of follow-up. A severe decline in nutritional status was defined as a decline of two or more points during the first 12 months of follow-up. We also explored the mean decline in SGA over the entire follow-up period, up to four years (median 1.6; IQR 0.9-2.4), in those with at least two SGA measurements.

Modifiable risk factors of interest

The determinants of interest were smoking, alcohol consumption, mental health, physical function and gastrointestinal symptoms. We used the research and development-36 (RAND-36) health questionnaire to assess patient-reported mental health and physical function (22, 23). It includes 36 items and 8 dimensions and is summarized into a physical- and a mental summary component score. The physical functioning part of RAND-36 includes questions about basic activities, such as self-care and house-work and is primarily reflected by the measures of physical functioning and pain. Mental health is primarily reflected by measures of emotional well-being, limitations caused by emotional problems and social functioning related to the ability to interact with family and friends (24). The physical component summary score (PCS) and mental component summary score (MCS) were calculated using norm-based scoring, which uses linear transformation to achieve standardized scores with a mean (SD) of 50 (10) for each dimension by using the US population as a reference group (25).

We analysed selected gastrointestinal symptoms from the validated Dialysis Symptom Index (DSI) (26). Patients had to score the presence of these symptoms over the past month. For each symptom present, patients rated symptom severity using a five-point scale with the options ‘not at all’, ‘a little bit’, ‘somewhat’, ‘quite a bit’ or ‘very much’. Information regarding smoking and alcohol was collected from the baseline patient questionnaire. Smoking habits were categorized as current smoker, former smoker, or never smoker. Alcohol consumption was categorized as drinker and non-drinker. For drinkers we collected the average number of unit’s alcohol per week.

Covariates

As a part of the study protocol, we collected information on demographics (age, sex, country), clinical information (primary renal disease, blood pressure, comorbidity, body mass index, waist circumference, eGFR), socio-economic status (level of education, marital status), and laboratory values (haemoglobin, albumin, renal function, and cholesterol). We used the Charlson comorbidity index (CCI) to adjust for comorbidity. The Charlson comorbidity index (CCI) was originally developed to predict mortality in longitudinal studies. The CCI consists of 17 comorbidities that are weighted from 1 to 6 for mortality risk and disease severity, and then summed to form a total score (27).

Statistics

The covariates and variables were described as means, medians and proportions according to their underlying distribution, both overall and by decline in SGA over 12 months. The distribution of age at inclusion was skewed and further categorized into five year intervals. Charlson comorbidity index was categorized into six approximately equally sized categories, and body mass index (BMI) was categorized into the World Health Organization classification modified according to geriatric guidelines suggesting BMI <22 kg/m^2 as

underweight. We categorized both the MCS and PCS into quartiles. Education was categorized into low (elementary school), intermediate (high school), high (college/university) and other (secondary schools).

The associations between potential risk factors and SGA decline were studied in different logistic regression models. Since there was a strong correlation between baseline SGA and SGA decline, we included SGA at baseline in our minimally adjusted models. We then additionally adjusted for age, sex and country (Model 1) and further with comorbidity, BMI, education, smoking and alcohol (Model 2). Since we regarded laboratory data an effect rather than the cause of nutritional status, we did not adjust for this in our models. Missing data was overall low (**Table S1**) and handled through multiple imputation with chained equations (10 repetitions) in which we included all variables related to demographics, anthropometrics, lifestyle, clinical data, comorbidity, RAND-36, laboratory data and outcome (SGA decline). Finally, we studied presence of effect modification between the exposures under interest and history of diabetes. All the analyses were performed with Stata 15 (StataCorp).

Results

In total, there were 1652 individuals included in the EQUAL study. We excluded 137 individuals without any SGA measurements, and another 412 individuals with less than two SGA measurements during follow-up. For the present analysis, we included 1103 older adults, not yet on dialysis. During the 12 months of follow-up 7% (77 individuals) started dialysis. The mean number of visits was 2.7. The mean follow-up time was 1.6 years, during which 24% (268 individuals) started dialysis. Baseline characteristics, in individuals with at least two measurements of 7-p SGA (n=1103) stratified on those with a decline in nutritional status or not within one year, are presented in **Table 1**. The median age was 76 years, 65% were male, and the median eGFR was 19 ml/min/1.73m². The majority of the patients had a normal nutritional status at baseline (SGA=7 [33.8%]; SGA=6 [38.1%]) while 28% were moderately malnourished (SGA ≤5). The mean SGA score was 6.0 at baseline.

Changes in nutritional status over time

Impaired nutritional status at one-year follow-up, was present in 385 individuals (34.9%). A severe decline in SGA occurred in 112 patients (10.9%). On the other hand an improvement in nutritional status (of at least 1 point in SGA) was seen in 254 individuals (23.5%). Over the entire follow-up period, up to 4 years (median 1.6 years, IQR 0.9-2.4) the mean SGA change was -0.18 points/year (95% CI -0.21; -0.14) (**Figure 1**).The proportion of patients with low SGA scores (1-5 points) increased by each six months, while those with SGA score 6-7 decreased. (**Figure 2**). Individuals who declined in SGA had a larger decrease in eGFR (mean change in eGFR -2.0 ml/min/1.73m [SD 0.27]) during follow-up compared to those with stable nutritional status (mean change in eGFR -0.7 ml/min/1.73m^2 [SD 0.2], p<0.001). There was no association between age, education, primary renal diagnosis and all the other variables shown in **Table S2** and SGA decline.

Life-style factors and nutritional status

Current smoking was a strong risk factor (OR 2.64; 1.50-4.64) for the worsening of nutritional status over one year, compared to both non-smoking and former smoking. The fully adjusted model showed an even stronger association (OR 3.25; 1.76-6.05) presented in **table 2**. The association between alcohol consumption and decline in SGA indicated a U-shaped relationship; a moderate consumption was associated with lower risk of SGA decline while a high alcohol consumption of more than 10 standard units/week suggested a higher risk of SGA decline, although not statistically significant **(Table 2)**.

Patient reported quality of life and nutritional status

At baseline, the mean mental component score was 48.7 (SD 10.7) in those with stable nutritional status after one year and 48.6 (SD 11.6) in the group who dropped in SGA. The mean physical component score was 35.7 (SD 11.1) and 33.1 (SD 11.2) in those with stable vs. declining SGA. Patients with a stable MCS during follow-up (mean change in MCS 0.10 [SD 9.0]) also had a stable nutritional status, while those who declined in MCS (mean change in MCS -1.92 [SD 10.6], p=0.03) also declined in SGA.

The MCS at baseline was not associated with a drop in SGA in the unadjusted or adjusted main analysis (**Table 3**). PCS, on the contrary, was associated with SGA decline by -1 point. Every 10 points higher PCS score at baseline decreased the odds of SGA decline by 23%. In a sensitivity analysis of severe decline in SGA, we observed similar associations for PCS, while every 10 point higher MCS now was associated with an 11% lower odds of severe SGA decline (**Table S3**). In patients with diabetes, the association of a low physical function score and SGA decline was more prominent, than in those without diabetes (**Table S4**).

Patient reported symptoms and nutritional status

At baseline, the study participants experienced several symptoms; 250 individuals (27%) reported decreased appetite, 267 (29%) reported constipation, 175 (19%) reported nausea, 231 (25%) diarrhoea and more than half the study participants (54%) reported a dry mouth (**Table 1**).

In the unadjusted analyses, the presence of most gastrointestinal symptoms was associated with a decline in SGA, although not statistically significant (**Table 3).** However, in the adjusted models constipation and decreased appetite were significantly associated. Sensitivity analyses of severe SGA decline yielded similar results (**Table S3**).

Discussion

In this large European study of older patients with advanced CKD we found that 28.0% of the patients was moderately malnourished at baseline, and 34.9% declined in SGA during 12 months of follow-up. A severe decline in nutritional status occurred in 10.9% of the study participants. We identified several characteristics associated with a higher risk of SGA decline; current smoking, low physical component score (PCS), constipation and decreased appetite were among those. The relationship between physical function and the risk of SGA decline was stronger in those with diabetes.

To the best of our knowledge, this is the first study to report changes in nutritional status over time in older patients with advanced CKD, not on dialysis. The mean SGA decline of -0.18 points/year indicates a progressive deterioration in nutritional status over time. Previously, weight has been used as a marker of nutritional status in studies of earlier stage CKD patients. In studies from the CRIC and AASK cohorts (28) a significant decline in weight occurred after eGFR decreased to <35 mL/min/1.73 m² and an annual weight loss >5% before dialysis therapy initiation was associated with a higher risk of all-cause mortality. The reasons for weight loss were not noted in these studies, but Kopple et al (29) found that patients with advanced CKD decrease their protein and energy intake as renal function deteriorates. They showed that the energy intake (calculated from diet records) was below the recommended level, particularly in those with a GFR <21 ml/min/1.73m² (29). Weight could be influenced by fluid retention, as oedema is common in advanced CKD (30). In the clinical setting, it may therefore be more relevant to screen for unintentional weight-loss, such as provided by the SGA tool, or measure body composition (31).

Our study shows that on a population level, many patients decline in nutritional status. Still, the majority did not deteriorate, and those with a stable nutritional status were also more

stable in the mental component score (MCS) and eGFR during follow-up. We additionally confirm that those with high comorbidities were at higher risk of a poor nutritional status and SGA decline (3, 32). All patients were treated by their nephrologist according to standard care in each country. Although we adjusted for factors, such as smoking and BMI, we were unable to adjust for referral patterns in the analysis, which might have affected the results.

Current smoking was a strong risk factor for deterioration in nutritional status over time. This finding adds to the many evidences of the harmful health effects of tobacco smoking. Healthcare should provide an anti-smoking program in CKD patients, not only to reduce the risk of cardiovascular events, but also to prevent worsening in nutritional status. A high alcohol intake was not associated with nutritional status deterioration in our study, but our results suggested that a low alcohol intake may be beneficial. However, this relationship was not consistent when looking at severe decline in SGA. Indeed, whereas KDIGO guidelines recommend stop smoking in their life-style chapter, they do not provide recommendations about alcohol consumption (33).

The patients of our cohort reported lower overall health-related quality of life as compared to the general population, but somewhat higher in comparison with studies of dialysis patients (34). In a large study of quality of life in individuals with ischemic heart disease (35), the mean PCS and MCS in patients >70 years were only slightly higher than the mean scores in our study. Similar to our study participants, they reported higher MCS than PCS. These findings support the hypothesis that older patients perceive less mental stress when they are confronted with disease, but are more prone to muscle wasting and poor physical status than younger patients (36, 37). Studies in hemodialysis patients have reported that individuals with diabetes have increased muscle breakdown compared to non-diabetic patients (38, 39). In accordance, we found an interaction with diabetes and physical function. Inflammation, sub-optimal metabolic control and sedentary life-style may contribute to this. Clinical studies

are needed to elucidate the role of poor metabolic control on muscle wasting and physical function in elderly persons.

In the present study, the MCS at baseline was not associated with decline in SGA, but those who declined in SGA also decreased in MCS. The cause and effect of these relationships may be difficult to disentangle in this observational study. However, if the associations are bidirectional, one could speculate on their relationships. Fatigue and lack of motivation may contribute to a poor diet and a worse nutritional status, while a deteriorated nutritional status could influence the mental health and health behaviour (40). We also found that low PCS is associated with a higher odds of SGA decline. Individuals with low PCS have similarities to the phenotype physical frailty (41), a low level of physical activity, weakness and exhaustion. From our data we cannot establish if interventions directed towards increased physical activity would change the risk for impaired nutritional status. However, guidelines already state that older persons at risk of malnutrition should be encouraged to be physically active and exercise in order to maintain or improve muscle mass and function (41, 42). This should be part of a multidisciplinary team intervention to improve functional and clinical outcome (43, 44).

Several studies report that the symptom burden in CKD is high (1, 45). In other publications from the EQUAL cohort, we have observed that the number and burden of symptoms increase progressively as renal function deteriorate (45). Moreover, a higher symptom burden has also been associated to a lower quality of life (2). In our present study we found that both constipation and decreased appetite were risk factors for decline in nutritional status. Constipation is prevalent in older adults and has previously been reported to be associated with poor appetite and nausea, factors that affect the energy- and nutrient intake (46). Using EQUAL data, Janmaat et al recently found that decreased appetite was the symptom that increased most severely over time in old adults with CKD. In our study, we observed that

those who declined in SGA, decreased more in mean eGFR compared to those with stable SGA. Since both eGFR and SGA were studied simultaneously we are unable to drawing any conclusions regarding the direction of this association, but we believe our finding suggest that at least some of the SGA decline could have been mediated by progressive kidney function loss. The prevalence of decreased appetite is twice as high in women as in men in older adults with CKD (1), which may explain why the association weakened when we first adjusted for sex. Surprisingly, dry mouth (xerostomia) was not a risk factor for impaired nutritional status. More than half of the study participants experienced this symptom, compared to 17-40% in studies of the geriatric population in general (46). However, xerostomia is the subjective feeling of a dry mouth, and is not always related to a reduced saliva flux (47).

Our study has several strengths. The cohort represents an incident European CKD cohort in six different countries with extensive demographic and clinical data. The nutritional assessment was performed by trained research nurses or dietitians in each country and all study centres participated in a standardized training program of the SGA method. We also acknowledge some limitations. Although the seven point SGA was developed for repeated measurements, there is a possibility that the method may misclassify individuals or be too insensitive to be able to identify more subtle changes over time. This would however only explain any lack of association. One limitation is the observational study design, where causal interpretations cannot be determined. Furthermore, life-style factors could be misclassified due to the design with self-reporting.

In conclusion, this European multicentre study with older, incident CKD patients shows that 34.9% displayed deterioration of nutritional status during one year of follow-up and on a population level the mean SGA decreased. Low health-related quality of life (especially the physical component), gastrointestinal symptoms (constipation and decreased appetite) and smoking were associated with deterioration in nutritional status. Future studies should explore

if specific interventions guided towards the risk groups will reduce the risk of SGA decline. Patient- reported outcome measures provide important information that could better guide health professionals towards a personalized approach.

Practical Application

Patient-reported measures influence the course of nutritional status in elderly people with CKD stage 4-5, not yet on dialysis. More than one-third of the study participants developed an impaired nutritional status during 1-year of follow-up. We identified that those with lower self-reported physical function, more gastrointestinal symptoms (particularly decreased appetite and constipation), and smokers were at higher risk of developing impaired nutritional status. These findings could guide health professionals towards a personalized approach.

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Table 1. Patient characteristics at baseline stratified by nutritional status decline within 12 months (n=1103)

Variables	**No decline in nutritional status** (n=718)	**Decline in nutritional status** (n=385)
Sex [n=1103]		
Male	468 (65.2)	244 (63.4)
Female	250 (34.8)	141 (36.6)
Age	76 (70-81)	76 (71-82)
Country [n=1103]		
Germany	55 (7.3)	19 (4.9)
Italy	166 (23.1)	76 (19.7)
Netherlands	73 (10.2)	22 (5.7)
Poland	21 (2.9)	12 (3.1)
Sweden	163 (22.7)	99 (25.7)
United Kingdom	240 (33.4)	157 (40.8)
Primary Renal Disease [n=1010]		
Glomerular disease	61 (9.4)	34 (9.4)
Tubulointerstitial disease	61 (9.4)	30 (8.3)
Systemic disease	259 (40.0)	143 (39.5)
Diabetes	137 (21.1)	75 (20.7)
Familial/hereditary nephropathies	27 (4.2)	12 (3.3)
Miscellaneous renal disorders	103 (15.9)	68 (18.8)

Clinical data		
eGFR mL/min/1.73² [n=1103]	19.3 (15.8-22.2)	19.9 (16.3-22.6)
Systolic blood pressure mmHg [n=1096]	142.5 (129-156)	144.3 (130-156)
Diastolic blood pressure mmHg [n=1096]	73.8 (67-80)	74.1 (67-81)
Body Mass Index kg/m² [n=1030]	28.3 (5.1)	28.7 (5.8)
Waist circumference, cm [n=1001]	103.4 (13.4)	104.8 (14.3)
SGA overall score [n=1103]	5.9 (1.0)	6.1 (0.9)
Comorbidity		
Charlson comorbidity index, mean (SD) [n=1086]	6.9 (1.8)	7.2 (1.9)
Diabetes mellitus [n=1087]	279 (39.6)	153 (40.1)
Psychiatric diseases [n=1081]	48 (6.9)	33 (8.7)
Cerebrovascular disease [n=1078]	105 (15.0)	56 (14.7)
Coronary artery disease [n=1064]	164 (23.8)	100 (26.7)
Heart failure [n=1067]	118 (17.0)	61 (16.4)
Pulmonary disease/asthma [n=1076]	104 (14.9)	65 (17.2)
Education [n=908]		
Low	183 (30.4)	108 (33.2)
Intermediate	306 (50.8)	152 (46.8)
High	85 (14.1)	46 (14.2)
Other	28 (4.7)	19 (5.9)
Marital status [n=906]		
Married/partner	387 (64.3)	202 (62.5)
Divorced/widowed/single	207 (35.5)	121 (37.5)

Lifestyle		
Smoking [n=886]		
Current smoker	43 (7.6)	45 (14.1)
Former smoker	308 (54.3)	181 (56.7)
Alcohol use, standard units/week [n=878]		
1-2	85 (51.1)	38 (12.1)
>2-6	93 (16.5)	41 (13.1)
>6-10	48 (8.1)	26 (8.3)
>10	38 (6.4)	25 (8.0)
RAND-36		
Mental Component Score [n=804]	48.7 (10.7)	48.6 (11.6)
Physical Component Score [n=804]	35.7 (11.1)	33.1 (11.2)
Symptoms		
Decreased appetite [n=907]	152 (26.1)	98 (30.3)
Constipation [n=920]	160 (27.0)	107 (32.6)
Nausea [n=909]	115 (19.7)	60 (18.5)
Diarrhoea [n=909]	147 (25.2)	84 (25.9)
Dry mouth [n=919]	318 (53.6)	180 (55.2)

Values are given as numbers (percentage), means (standard deviation) or median (interquartile range).

Table 2. Life-style factors and risk for nutritional status deterioration

Life-style factor	Minimally adjusted* OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Smoking			
Never smokers	1.0	1.0	1.0
Former smokers	1.38 (0.98-1.93)	1.51 (1.06- 2.16)	1.41 (0.94-2.11)
Current smokers	2.64 (1.50- 4.64)	2.88 (1.60- 5.19)	3.26 (1.76- 6.05)
Alcohol consumption (standard units/week)	*P-trend 0.09*	*P trend 0.41*	*P trend 0.33*
None	1.0	1.0	1.0
1-2	0.66 (0.44-0.99)	0.67 (0.47-0.96)	0.61 (0.42-0.90)
>2-6	0.65 (0.48-0.88)	0.65 (0.49-0.87)	0.66 (0.45-0.97)
>6-10	0.84 (0.67-1.06)	0.86 (0.67-1.10)	0.67 (0.52-0.86)
>10	1.06 (0.66-1.68)	1.09 (0.64-1.85)	1.13 (0.54-2.38)

*Minimally adjusted (adjusted for baseline SGA)

Model 1 adjusted for SGA baseline, age, sex, and country

Model 2 additionally adjusted for comorbidity, BMI, education, mental summary score, physical summary score and (smoking/alcohol)

Table 3. Patient-reported measures and risk of nutritional status deterioration

Patient-reported measures	Minimally adjusted* OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Mental Component Summary, per 10 p increase	0.96 (0.85-1.08)	0.96 (0.87-1.07)	1.03 (0.95-1.11)
Mental Component Summary			
≥ 56.7	1.0	1.0	1.0
<56.7-50.9	0.9 3(0.70-1.23)	0.93 (0.69-1.24)	0.76 (0.50-1.13)
<50.9-40.5	0.92 (0.70-1.22)	0.92 (0.69-1.24)	0.68 (0.49-0.95)
<40.5	1.15 (0.86-1.54)	1.14 (0.88-1.47)	0.88 (0.68-1.12)
Physical Component Summary, per 10 p increase	0.77 (0.69-0.86)	0.76 (0.70-0.81)	0.77 (0.67-0.87)
Physical Component Summary			
≥43.7	1.0	1.0	1.0
< 43.7-34.6	1.13 (0.93-1.36)	1.13 (0.93-1.36)	1.05 (0.88-1.26)
<34.6-26	1.30 (0.95-1.79)	1.35 (1.05-1.73)	1.22 (0.90-1.68)
<26.0	2.02 (1.49-2.72)	2.08 (1.58-2.76)	2.02 (1.35-3.02)
Symptoms			
Decreased appetite	1.50 (0.93-2.42)	1.47 (0.89-2.44)	1.56 (1.06-2.28)

Constipation	1.36 (1.22-1.52)	1.36 (1.21-1.53)	1.41 (1.20-1.67)
Nausea	1.00 (0.90-1.24)	0.98 (0.77-1.24)	1.06 (0.83-1.36)
Dry mouth	1.10 (0.75-1.60)	1.08 (0.71-1.65)	1.04 (0.73-1.68)
Diarrhoea	1.13 (0.90-1.41)	1.12 (0.90-1.39)	1.05 (0.74-1.48)

*Minimally adjusted (adjusted for baseline SGA)

Model 1 adjusted for SGA baseline, age, sex, and country (cluster)

Model 2 additionally adjusted for comorbidity, BMI, education, and (smoking/alcohol)

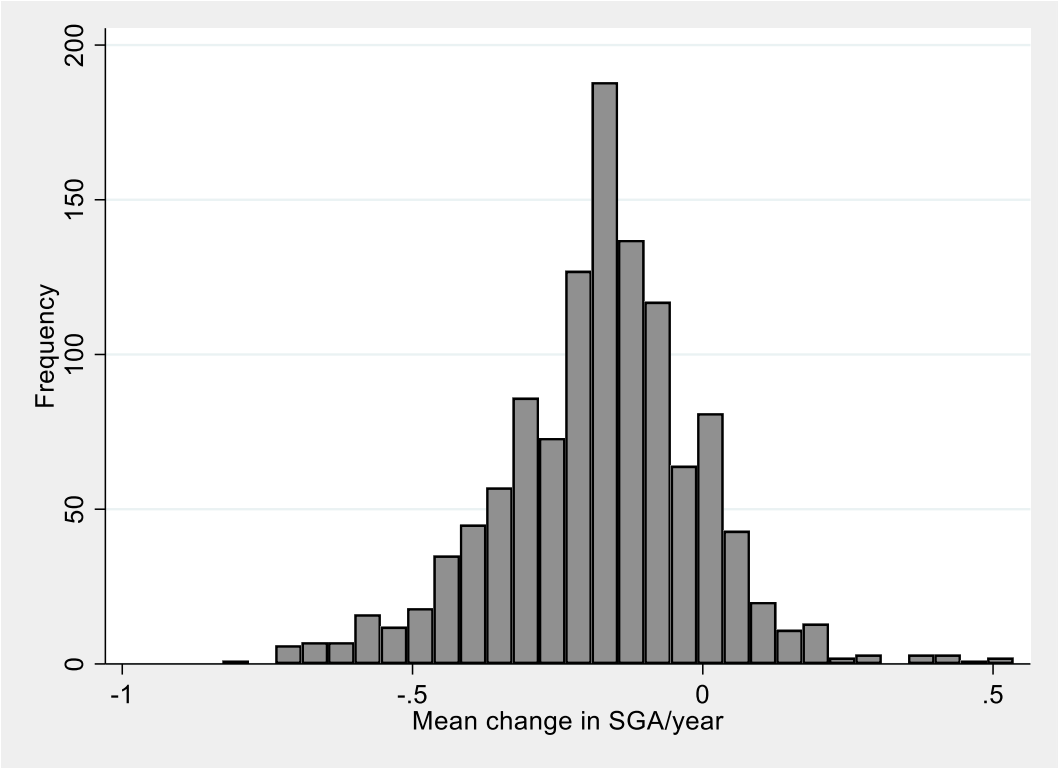

Figure 1. Mean change in SGA (points/year) during the entire follow-up period, up to four years.

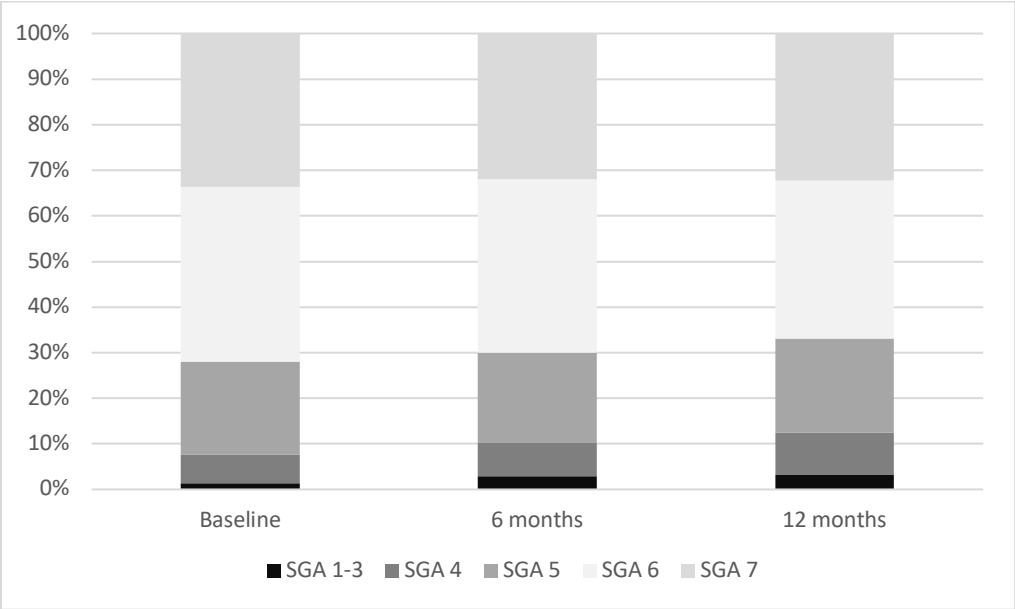

Figure 2. Cross-sectional prevalence and distribution of 7-p SGA scores at baseline (n=1103), 6 months of follow-up (n=1011) and 12 months (n=793).