The role of inflammation in muscle aging

Beenakker, K.G.M.

Chapter 2

Patterns of muscle strength loss with age in the general population and patients with a chronic inflammatory state

Published as: K.G.M. Beenakker, C.H. Ling, C.G.M. Meskers, A.J.M. de Craen, Th. Stijnen, R.G.J. Westendorp, A.B. Maier, *Ageing Research Reviews* **9** (2010) 431–436.

Abstract

Background: There is growing recognition of the serious consequences of sarcopenia on the functionality and autonomy in old age. Recently, the age-related changes in several inflammatory mediators have been implicated in the pathogenesis of sarcopenia. The purposes of this systematic review were two-fold: (1) to describe the patterns of muscle strength loss with age in the general population, and (2) to quantify the loss of muscle strength in rheumatoid arthritis as representative for an underlying inflammatory state. Handgrip strength was used as a proxy for overall muscle strength.
Results: Results from 114 studies (involving 90,520 subjects) and 71 studies (involving 10,529 subjects) were combined in a meta-analysis for the general and rheumatoid arthritis population respectively and standardized at an equal sex distribution. For the general population we showed that between the ages of 25 years and 95 years mean handgrip strength declined from 45.5 kg to 23.2 kg for males and from 27.1 kg to 12.8 kg for females. We noted a steeper handgrip strength decline after 50 years of age (rate of 0.37 kg/year). In the rheumatoid arthritis population handgrip strength was not associated with chronological age between the ages of 35 years and 65 years and was as low as 20.2 kg in male and 15.1 kg in female. Rheumatoid arthritis disease duration was inversely associated with handgrip strength.
Conclusions: This meta-analysis shows distinct patterns of age-related decrease of handgrip strength in the general population. Handgrip strength is strongly associated with the presence and duration of an inflammatory state as rheumatoid arthritis. The putative link between age-related inflammation and sarcopenia mandates further study as it represents a potential target for intervention to maintain functional independence in old age.

2.1 Introduction

Sarcopenia, age-related loss of muscle mass and strength, is highly prevalent, with reported proportions exceeding 50% in those aged 80 years and older (Iannuzzi-Sucich, Prestwood & Kenny, 2002; Baumgartner *et al.*, 1998). This ageing phenomenon is becoming an important public health concern as it inflicts a profound functional burden on our growing elderly population and contributes to increased morbidity (Rantanen, Era & Heikkinen, 1994; Rantanen *et al.*, 1999; Taekema *et al.*, 2010) and mortality (Rantanen *et al.*, 2000; Metter *et al.*, 2002; Ling *et al.*, 2010). Several studies have shown that loss

of muscle mass occurs as early as the fifth decade of life and accelerates in older age (Lexell, Downham & Sjöström, 1986; Janssen *et al.*, 2000). The etiology and pathogenesis of sarcopenia is complex and probably involves the interplay of a myriad of factors including physical inactivity, hormonal, metabolic and nutritional factors (Doherty, 2003; Morley *et al.*, 2001). Recent research has also implicated age-related changes in several inflammatory mediators in the pathogenesis of sarcopenia (Krabbe, Pedersen & Bruunsgaard, 2004).

Similar to the ageing process, inflammatory cytokines have been shown to have a profound role in the pathogenesis of "rheumatoid cachexia", the loss of muscle mass and strength with concomitant increase in fat mass, which persists after joint inflammation improves in rheumatoid arthritis (RA) patients (Roubenoff, 2009). In patients with chronic inflammatory diseases such as RA, there is an accelerated loss of muscle mass and strength compared to healthy subjects (Roubenoff, 2000; Madhok *et al.*, 1993).

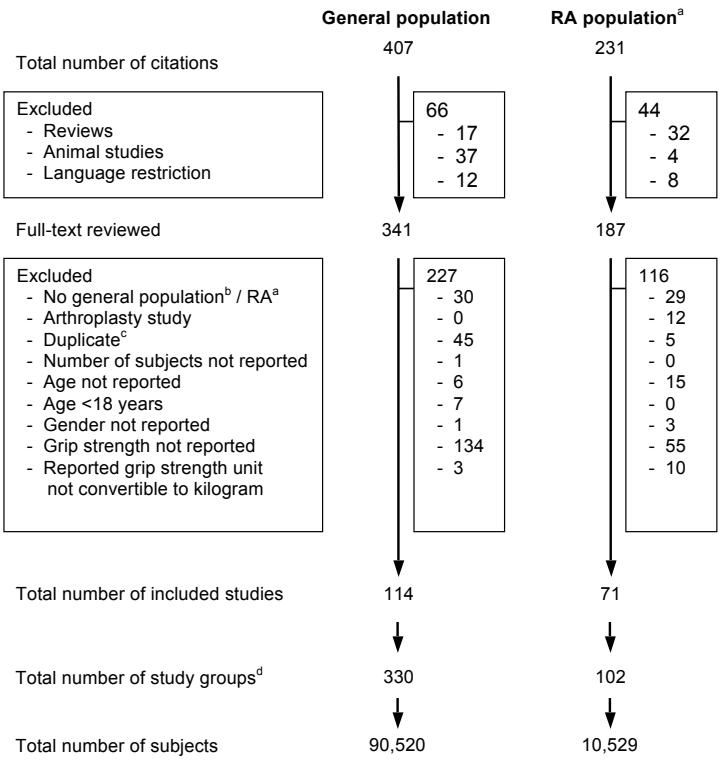
Although sarcopenia research has intensified in recent years, a general overview on the patterns of muscle strength loss with age and chronic inflammation is lacking. The aims of this quantitative systematic review were to describe the patterns of handgrip strength (HGS) loss with age in the general population and to quantify the loss of strength in a chronic inflammatory state such as RA.

2.2 Methods

2.2.1 Selection of studies

We conducted a search of the literature using MESH terms "hand strength", "rheumatoid arthritis" and "ageing" from the MEDLINE database from January 1999 to January 2009. The search was limited to human studies and reports published in English, French, German, Italian or Dutch. Review articles with duplicate data were excluded. The search yielded 528 citations. The article selection process is illustrated in Figure 2.1.

One investigator (K.B.) reviewed all potentially relevant articles in full text. If eligibility was questionable (15% of all articles), articles were discussed with a second investigator (A.M.). Criteria for final inclusion in the systematic review were (1) HGS measurements were performed in subjects representative for the general population or subjects with RA; (2) HGS was measured by a hand-held dynamometer with results reported in kilogram (kg), Newton



[a] RA: rheumatoid arthritis
[b] Studies reporting on admitted subjects or with specific diseases
[c] Studies reporting on a same cohort
[d] Study groups are defined as whole study groups or sub-study groups based on gender, age-categories or study specific sub grouping.

Figure 2.1. Summary of article selection process.

(N) or pound (lb) or a sphygmomanometer with results reported in mmHg or kilo-Pascal and (3) data on sample size, age and gender were available. There were no nationality or ethnicity related selection criteria.

Studies performed exclusively in patients from hospital wards or rehabilitation clinics were excluded as well as those including diseases or conditions that may affect HGS such as osteoarthritis, diabetes, growth hormone or testosterone deficiencies, osteoporosis, severe acute respiratory syndrome, renal failure, neuromuscular disorders (including stroke, dementia and Parkinson's disease), and wrist arthroplasty. Studies with other forms of inflammatory arthritis in the study populations were only included if HGS

measurements were either specifically described for the RA subjects or the RA subjects represented over 75% of the study population.

2.2.2 Data extraction

The following information was extracted from each article: year of publication, sample size, mean and standard deviation (SD) of HGS, age and gender distribution. Whenever available, anthropometrical data, RA disease duration, pain-scores (as measured on the visual analogue scale (VAS)), general health (as measured on the health assessment questionnaire (HAQ)), inflammatory markers (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) were also extracted. When HGS measurements were reported separately for male and female or for different age categories or other study specific sub-grouping, these measurements were regarded as being distinct study groups. Therefore, multiple study groups were extracted from the original articles. In case the age category was reported as range without the mean age, the midpoint of the age range was used for the analysis. Study groups were excluded when no lower or upper age cut-off was described for the age category. For longitudinal studies, only baseline data were selected and HGS measurements reported on subjects who died during the study follow-up duration were excluded.

If necessary, data were converted into kg equivalent: newtons (N) were divided by 9.81; pounds (lb) by 0.45; units of pressure (mmHg) or force (kPa) were converted using validated methods (Desrosiers *et al.*, 1995; Agnew & Maas, 1991). In studies where only the mean HGS was reported without the SD, the latter was estimated based on the linear regression of the variance of HGS on the mean HGS using the groups that provided complete data (mean and SD) for the general or RA population.

2.2.3 Statistical analysis

To determine the mean HGS at different calendar ages in the general and RA population, we performed random effects meta-regression analyses adjusted for age and gender (Van Houwelingen, Arends & Stijnen, 2002). These meta-regression models allowed us to make tables and figures for study groups standardized at 50% females or for males and females separately. For the general population, we first ascertained by eyeballing the scatter plot a change point at which the slope of annual decrease in HGS changed

most rapidly. This change point parameter was then included in the meta-regression analysis as described by Samson *et al.* (2000). To further extend the meta-regression models for both the general and RA population, the method of forward selection was used. We first selected the significant squared terms from the continuous independent variables and then the significant interaction terms. For the meta-regression model of the general population, this resulted in inclusion of the gender x age interaction term in the analysis. This interaction indicated that the relation between HGS and age was dependent on the gender distribution. We plotted this relationship standardized at an equal sex distribution. For the RA population, none of the squared terms or interaction terms were significant and therefore, no further extension of the model was needed. Similarly, the method of forward selection was used in the analysis of HGS and RA disease duration, adjusted for age and gender. This resulted in inclusion of disease duration x age interaction to the meta-regression model. Again, the meta-regression line of this model was only plotted for the case of an equal sex distribution. All statistical analyses were performed in STATA 10. In all meta-analyses the groups were assumed to be independent, i.e. no allowance was made for groups coming from the same study.

2.3 Results

Out of 114 studies related to HGS in the general population we extracted 330 study groups involving 90,520 subjects. For RA, 102 study groups were extracted from 71 studies involving 10,529 subjects (Figure 2.1). In the general population, HGS was measured using a hand-held dynamometer in 99.7% of the study groups and a sphygmomanometer in 0.3%, compared to 61.7% and 38.3%, respectively of the study groups in the RA population. Standard deviation of the mean HGS was reported in 82.1% and 79.4% of the study groups for the general and RA population, respectively.

Table 2.1 shows the characteristics of the extracted study groups for the two populations apart. The median number of subjects per study group was 50.5 in the general population and 47.0 in the RA population. The age range of subjects within all study groups in the general population was 20–100 years (median 65.0) and in the RA population 31–65 years (median 55.1). Clinical parameters (VAS and HAQ scores) and inflammatory markers (CRP and ESR) were reported more frequently in the RA population compared to the general population. The RA population had higher pain score, poorer

Table 2.1. Descriptive statistics of extracted means from study groups included in the review. Study groups derived from 114 studies (330 study groups) of the general population and 71 studies (102 study groups) of the rheumatoid arthritis (RA) population.

	General population		RA population	
	N	median (IQR)	N	median (IQR)
Total number subjects		90,520		10,529
Number of subjects per study group		50.5 (19-189)		47 (20-100)
Age, years	330	65.0 (50.5-75.7)	102	55.1 (50.0-57.5)
Age SD per study group, years	169	5.2 (3.0-7.8)	73	12.0 (10.0-13.0)
Gender, % females	330	54.6 (0-1)	102	77.1 (69.0-87.0)
Disease duration, years	-	-	88	7.8 (2.6-12.5)
Anthropomorphic measurements				
Height, cm	150	163.3 (158.0-172.5)	14	165.5 (164.0-169.0)
Weight, kg	153	66.7 (58.1-76.4)	14	70.8 (67.5-74.0)
BMI, kg/m²	195	25.0 (23.0-26.6)	15	26.0 (25.2-27.4)
Clinical measurements				
Pain, VAS 0-100	3	2 (0-11.5)	51	45.2 (32.0-54.0)
HAQ, 0-3	3	0.05 (0-0.07)	40	1.18 (0.88-1.34)
Inflammatory markers				
CRP, mg/L	8	2.98 (1.0-6.7)	31	22.0 (11.5-32.0)
ESR, mm/h	1	8.8 (-)	51	34.0 (25.0-47.6)

Data are presented as medians with 25th and 75th percentiles (i.e. interquartile ranges [IQR])
N: number of study group with available data. Study groups are defined as whole study groups or sub-study groups based on gender, age categories or study specific sub-grouping.
BMI: body mass index, VAS: visual analogue scale, HAQ: health assessment questionnaire.

general health and elevated inflammatory markers compared to the general population. RA disease duration was reported for 86% of the RA study groups.

Table 2.2 shows the mean HGS values according to age for the general and RA population standardized for males and females separately. In the general population, HGS diminished gradually with age, with a change point at age 50 years after which there was a steeper decline in HGS (Table 2.3 and Figure 2.2). The annual decline of HGS loss was 0.06 kg from age 20 years to 50 years and 0.37 kg from 50 years onwards. In the RA population, HGS values were much lower compared to that of the general population of similar age range. In fact, they were comparable to that of the oldest old in the general population. No association was noted between chronological age and HGS in the RA population (Table 2.3 and Figure 2.3A). However, RA disease duration was significantly associated with a decline in HGS over time, with an annual rate of loss of 0.34 kg at age 55.6 years (95% CI: -0.58 to -0.10) (Figure 2.3B).

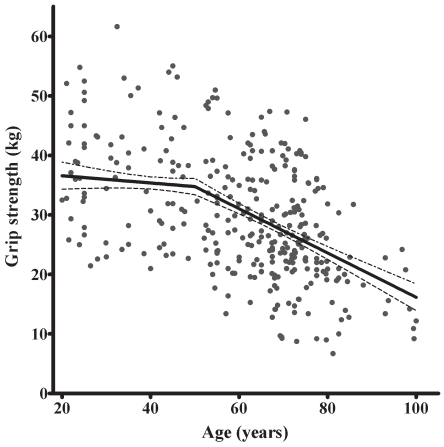


Figure 2.2. Handgrip strength in the general population dependent on age. Scatter plot of study groups from the general population (n = 330) and meta-regression lines with 95% confidence band (standardized at 50% females) with a change point at the age of 50 years.

The availability of additional characteristics, such as anthropomorphic measurements and inflammatory markers was too small to adjust for in the final analysis for the general and RA population. However, when the adjustment was performed on height and weight in the general population, results did not change significantly (data not shown).

2.4 Discussion

We performed meta-regression analyses to evaluate the patterns of HGS loss with age in the general population and quantified the magnitude of strength loss when chronic inflammation is present, using RA as a representative condition. HGS was used as a proxy for overall muscular strength as it has been shown to correlate well with whole body muscle strength [3]. It is also an easily accessible, simple and reliable clinical assessment tool (Innes, 1999). We found an inverse relationship between HGS and age, with a gradual decline starting as early as the third decade of life followed by a steeper deterioration after 50 years of age. Subjects with RA had significantly lower handgrip strength compared to the general population of similar age. HGS was also associated with disease duration of RA. To the best of our knowledge, this

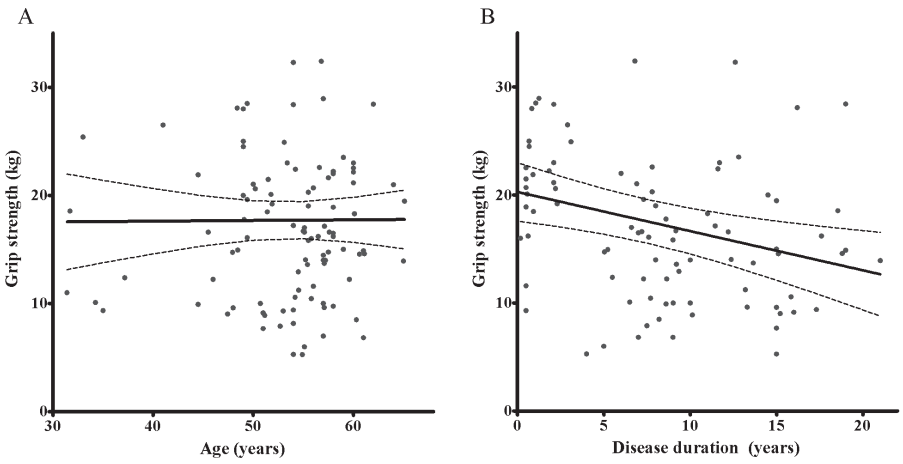


Figure 2.3. Grip strength in rheumatoid arthritis (RA) population dependent on age (n = 102) and RA disease duration (n = 88). (A) Scatter plot of study groups in the RA population dependent on chronological age and meta-regression line with 95% confidence band (standardized at 50% females). (B) Scatter plot of study groups in the RA population dependent on disease duration and meta-regression curve with 95% confidence band standardized at 50% females at median chronological age 55.1 years.

study provides the first large sample systematic review of the patterns of loss of muscle strength in the general as well as the in the RA population over a wide age range.

The data from our study on the pattern of HGS loss in the general population support the curvilinear relationship between HGS and age as reported in some earlier published studies (Vianna, Oliveira & Araújo, 2007; Rantanen *et al.*, 1998). In women, the rapid decline in HGS after 50 years of age has been linked to sex hormone deficiency occurring at menopause and lifestyle changes during the transition (Samson *et al.*, 2000; Vianna, Oliveira & Araújo, 2007). In men however, the profile of strength loss is less well established (Metter *et al.*, 2002; Samson *et al.*, 2000; Vianna, Oliveira & Araújo, 2007). Nonetheless, the rate of HGS decline in the general population of this study comprising of 50% females was comparable to that reported by Rantanen *et al.* (1998).

We also found that HGS in middle-aged RA subjects was approximately half that of the general population. This finding supports previous observations on the negative effects of chronic inflammation on muscle function (Van

Table 2.2. Handgrip strength (kg) in the general population and rheumatoid arthritis (RA) population dependent on age for male and female.

	General population[a]		RA population[b]	
	Male	Female	Male	Female
Age (years)	mean in kg (95% CI)	mean in kg (95% CI)	mean in kg (95% CI)	mean in kg (95% CI)
25	45.5 (43.2; 47.8)	27.1 (24.4; 29.7)	-	-
35	44.3 (42.7; 45.9)	27.0 (25.2; 28.8)	20.2 (15.0; 25.3)	15.0 (11.2; 18.9)
45	43.1 (41.7; 44.6)	27.0 (25.5; 28.5)	20.2 (16.1; 24.4)	15.1 (12.7 ; 17.4)
55	40.4 (39.1; 41.8)	25.4 (24.1; 26.7)	20.3 (16.4; 24.2)	15.1 (13.3; 16.9)
65	36.1 (35.0; 37.2)	22.3 (21.2; 23.3)	20.4 (16.0; 24.7)	15.2 (12.4; 18.0)
75	31.8 (30.5; 33.2)	19.1 (17.9; 20.3)	-	-
85	27.5 (25.6; 29.5)	16.0 (14.2; 17.7)	-	-
95	23.2 (20.6; 25.8)	12.8 (10.4; 15.2)	-	-

Grip strength in kg of each age is standardized for male and female.
[a] Meta-regression model with change point at age 50 years.
[b] Linear meta-regression model.
CI: confidence interval.

Table 2.3. Change in handgrip strength (kg) per calendar year in the general population and rheumatoid arthritis (RA) population.

	General population[a]		RA population[b]	
	Age range in years	mean (95% CI)	Age range in years	mean (95% CI)
Change of grip strength (kg/y)	20-50	-0.06 (-0.16; 0.04)	31-65	0.01 (-0.18; 0.19)
	50-100	-0.37 (-0.44; -0.31)		

Standardized at 50% females.
[a] Meta-regression model with change point at age 50 years.
[b] Linear meta-regression model.
CI: confidence interval.

Hall *et al.*, 2008; Bodell *et al.*, 2009). Few studies have reported the crucial role of "sarcoactive" cytokines such as TNF-α and IL-6 and CRP in the pathogenesis of RA (Madhok *et al.*, 1993; Choy & Panayi, 2001; Engvall *et al.*, 2008). These pro-inflammatory cytokines have also been implicated in the pathogenesis of sarcopenia in "normal" ageing (Schaap *et al.*, 2009).

In RA subjects loss of muscle strength was already observed before the age of 50 years. This supports the concept of RA being a disease of accelerated aging. Recenty it has been shown that RA patients suffer from excess ageing occurring prior to RA incidence as well as an acceleration of aging (Schaap *et al.*, 2009). We postulate that the loss of muscle strength early in life of RA subjects is one of the aspects behind this phenomenon.

Our quantitative analysis of the literature has several limitations. First, there is the limitation due to using aggregate data (study groups) instead of data of individuals. However, the variance that is lost by aggregating individu-

als into study groups in the general population is limited, because the median SD of age for the study groups is calculated to be only 5.2 years, which is small compared to the between studies variance in mean age. In RA the median SD of age was higher (12.0 years) which could have led to an underestimation of the effect of age on HGS. Despite of aggregating, the statistical heterogeneity between study groups was high. This might be caused by differences between studies in factors such as method of HGS measurement, body composition and ethnicity and in the RA population also by RA disease duration and medication use.

We were unable to directly assess the influence of inflammation on HGS in the RA subjects as we did not account for various other factors that could affect HGS measurements such as pain or fear of pain, stiffness, corticosteroid use, disuse atrophy and mechanical disruption. Furthermore, in the RA population, we observed an inverse association between HGS and duration of RA disease but not the influence of chronological age per se. This could in part be explained by selection as RA subjects with profound muscle weakness were less likely to participate in studies and had higher mortality due systemic disease. Still, the amount of inflammatory pressure during the ageing process is low when compared to RA (Madhok *et al.*, 1993). We showed that at the moment of RA diagnosis mean HGS is already as low as 20 kg. This implies that the impact of chronic inflammation on HGS was the highest already during the months from the earliest onset of RA and at the moment of diagnosis, which normally goes together with the start of an anti-inflammatory treatment (Morel & Combe, 2005). For the period after diagnosis we showed RA to be associated with remarkable elevated level of inflammatory markers ESR and CRP.

This meta-analysis confirms previously reported patterns of age-related decrease of HGS in the general population. The putative link between age-related inflammation and sarcopenia mandates further exploration. Investigating RA may serve as representative condition when studying inflammatory pathways that lead to sarcopenia, which are relatively subtle in the general population. These pathways, however represent a potential target for intervention to prevent disability and maintain functional independence in old age.