Ageing Research Reviews 31 (2016) 1–8

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Review

Inflammation and frailty in the elderly: A systematic review and meta-analysis

Pinar Soysal (M.D.)[a,1], Brendon Stubbs (Ph.D.)[b,c,t,1], Paola Lucato (M.D.)[d,1], Claudio Luchini (M.D.)[e], Marco Solmi (M.D.)[f,g,h], Roberto Peluso (M.D.)[i], Giuseppe Sergi (MD)[j], Ahmet Turan Isik (M.D.)[k], Enzo Manzato (M.D.)[l], Stefania Maggi (M.D.)[m], Marcello Maggio (M.D.)[n], A. Matthew Prina (Ph.D.)[o], Theodore D. Cosco (Ph.D.)[p], Yu-Tzu Wu (Ph.D.)[q], Nicola Veronese (M.D.)[r,s,*]

[a] *Center for Aging Brain and Dementia, Department of Geriatric Medicine, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey*
[b] *Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London SE5 8AZ, United Kingdom*
[c] *United Kingdom and Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London Box SE5 8AF, United Kingdom*
[d] *Geriatrics Section, Department of Medicine (DIMED), University of Padova, Padova, Italy*
[e] *Department of Pathology and Diagnostics, University and Hospital Trust of Verona, Verona, Italy*
[f] *Department of Neurosciences, University of Padova, Padova, Italy*
[g] *Local Health Unit 17, Mental Health Department, Padova, Italy*
[h] *Institute of Clinical Research and Education in Medicine (IREM), Padova, Italy*
[i] *Geriatrics Section, Department of Medicine (DIMED), University of Padova, Padova, Italy*
[j] *Geriatrics Section, Department of Medicine (DIMED), University of Padova, Padova, Italy*
[k] *Center for Aging Brain and Dementia, Department of Geriatric Medicine, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey*
[l] *Geriatrics Section, Department of Medicine (DIMED), University of Padova, Padova, Italy*
[m] *Aging Branch, Institute of Neuroscience, National Research Council-CNR, Padova, Italy*
[n] *Geriatric Clinic and Laboratory of Movement Analysis, Geriatric and Rehabilitation Department, University Hospital of Parma, Via Gramsci 14, I-431126 Parma, Italy*
[o] *King's College London, Centre for Global Mental Health, Health Service and Population Department, Institute of Psychiatry, Pscyhology and Neuroscience, De Crespigny Park, SE5 8AF London, United Kingdom*
[p] *MRC Unit for Lifelong Health & Ageing, University College London, 33 Bedford Place, London WC1B 5JU, United Kingdom*
[q] *REACH: The Centre for Research in Aging and Cognitive Health, College of Life and Environmental Sciences—Psychology, University of Exeter, Exeter EX4 4QG, United Kingdom*
[r] *Nicola Veronese, Geriatrics Section, Department of Medicine (DIMED), University of Padova, Padova, Italy*
[s] *Institute of Clinical Research and Education in Medicine (IREM), Padova, Italy*
[t] *Health, Social Care and Education, Anglia Ruskin University, Chelmsford, UK*

ARTICLE INFO

Article history:
Received 5 June 2016
Received in revised form 8 August 2016
Accepted 24 August 2016
Available online 31 August 2016

Keywords:
Inflammation
Pre-frailty
Frailty
Aging
C-Reactive protein
Interleukin-6

ABSTRACT

The pathogenesis of frailty and the role of inflammation is poorly understood. We examined the evidence considering the relationship between inflammation and frailty through a systematic review and meta-analysis. A systematic literature search of papers providing data on inflammatory biomarkers and frailty was carried out in major electronic databases from inception until May 2016. From 1856 initial hits, 35 studies (32 cross-sectional studies n = 3232 frail, n = 11,483 pre-frail and n = 8522 robust, and 563 pre-frail + robust; 3 longitudinal studies n = 3402 participants without frailty at baseline) were meta-analyzed. Cross-sectional studies reported that compared to 6757 robust participants, both 1698 frail (SMD = 1.00, 95%CI: 0.40–1.61) and 8568 pre-frail (SMD = 0.33, 95%CI: 0.04–0.62) participants had significantly higher levels of C-reactive protein (CRP). Frailty (n = 1057; SMD = 1.12, 95%CI: 0.27–2.13) and pre-frailty (n = 4467; SMD = 0.56, 95%CI: 0.00–1.11) were associated with higher serum levels of interleukin-6 compared to people who were robust (n = 2392). Frailty and pre-frailty were also significantly associated with elevated white blood cell and fibrinogen levels. In three longitudinal studies, higher

* Corresponding author at: University of Padova, Department of Medicine (DIMED)-Geriatrics Section, Via Giustiniani, 2, 35128 Padova, Italy.
E-mail address: ilmannato@gmail.com (N. Veronese).
[1] These authors equally contributed to this research.

http://dx.doi.org/10.1016/j.arr.2016.08.006

serum CRP (OR = 1.06, 95%CI: 0.78–1.44,) and IL-6 (OR = 1.19, 95%CI: 0.87–1.62) were not associated with frailty. In conclusion, frailty and pre-frailty are associated with higher inflammatory parameters and in particular CRP and IL-6. Further longitudinal studies are needed.

Contents

1. Introduction 2
2. Materials and methods 2
2.1. Search strategy 2
2.2. Study selection 2
2.3. Data extraction 3
2.4. Outcomes 3
2.5. Assessment of study quality 3
2.6. Statistical analysis 3
3. Results 3
3.1. Study and patient characteristics 3
3.2. Cross-sectional meta-analysis findings 4
3.3. Meta-regression and sensitivity analyses 4
3.4. Longitudinal meta-analysis findings 4
3.5. Publication bias 5
4. Discussion 5
Conflict of interest 6
Financial disclosure 6
Acknowledgments 6
Appendix A. Supplementary data 6
References 6

1. Introduction

Age-associated decline in reserve and function may result in a reduced ability to cope with acute or external stressors faced every day, which is typically defined as frailty (Clegg et al., 2013). Frailty is a relevant issue in geriatric medicine, since frailty is associated with a higher risk of poor outcomes such as falls, depression, disability, and mortality (Fried et al., 2001). Frailty is becoming one of the most significant clinical conditions affecting older people, with a prevalence of 10% for those older than 65 years and 30% for those older than 80 years (Fried et al., 2001).

Despite an increase in interest in frailty, the pathophysiological changes underlying and preceding frailty are not clearly known. Inflammation is one such potential pathophysiological change which may be closely linked with frailty (Chen et al., 2014). Pro-inflammatory cytokines may influence frailty either directly by promoting protein degradation, or indirectly by affecting important metabolic pathways (Lang et al., 2009). A direct association between frailty and elevated levels of inflammation, as marked by elevated interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen, and factor VIII, independent of common chronic disease states has been observed (Newman et al., 2001). Conversely, other studies have found that these markers are not predictive of incident frailty in the elderly (Yao et al., 2011). Thus, there is a lack of clarity considering the role and status of inflammation in frailty and to the best of our knowledge, no meta-analysis has attempted to synthesize the available data on this topic.

Therefore, we conducted a systematic review and meta-analysis comparing the inflammatory profile of frail and pre-frail with and robust subjects in cross sectional studies. In addition, we investigated whether or not any inflammatory parameters at baseline could predict the onset of frailty in prospective studies. Our hypothesis was that both frailty and pre-frailty were associated with higher pro-inflammatory cytokines levels.

2. Materials and methods

This systematic review was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] criteria (von Elm et al., 2008) and the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] statement (Liberati et al., 2009). This work followed a pre-determined, but unpublished protocol available upon request.

2.1. Search strategy

Three independent authors (PS, BS and NV) searched Medline (via Ovid), Psychinfo and EMBASE for studies from inception until 05/2016 without language restrictions. The search terms used were (frailty OR frail) AND ((“inflammation”[MeSH Terms] OR “inflammation”[All Fields]) OR inflammatory[All Fields] OR IFN [All Fields] OR (“interferons”[MeSH Terms] OR “interferons”[All Fields] OR “interferon”[All Fields]) OR TNF [All Fields] OR “tumor necrosis factor”[All Fields] OR IL[All Fields] OR “interleukin”[All Fields] OR “TGF”[All Fields] OR (“apoptosis”[MeSH Terms] OR “apoptosis”[All Fields]) OR apoptotic[All Fields] OR antiapoptotic [All Fields] OR CRP[All Fields] OR (“cytokines”[MeSH Terms] OR “cytokines”[All Fields] OR “cytokine”[All Fields])).

2.2. Study selection

Included studies were those that were published quantitative studies of a cross sectional or longitudinal design that (1) reported on serum levels of inflammatory parameters, (2) used a validated and standardized method for assessing frailty, (3) included a control group (pre-frail and robust as separated entities or together): (4) used serum inflammatory parameters as predictors of frailty

(longitudinal design). Studies were excluded if they (1) did not use a clear diagnostic criteria for frailty or used only one item for its diagnosis (e.g. low gait speed), (2) measured only in vitro parameters, (3) did not measure or did not report quantitative cytokine levels.

2.3. Data extraction

To be included in the quantitative analyses, we required data on serum inflammatory parameters in frail, pre-frail and robust participants expressed as means ± standard deviation (SD) or median with range (or interquartile range).

Two authors (PS, NV) independently extracted data from the selected studies in a standardized Microsoft Excel spreadsheet. Any disagreement was resolved by through discussion with a third author (BS). The following information was extracted: (i) characteristics of the study population (e.g. sample size, demographics, country in which the study was performed); (ii) setting in which the study was performed; (iii) diagnostic criteria for frailty; (iv) inflammatory parameters assessed with correspondent method of measurement; (v) demographic characteristics (mean age and percentage of women) and mean body mass index (BMI) by frailty status; (v) categorization used for dividing the sample in groups by serum inflammatory levels (for longitudinal studies); (vi) type and number of adjustments in the multivariate analyses (for longitudinal studies); (vi) follow-up period (only for longitudinal studies).

When information on frailty and/or serum inflammatory parameters was missing, study authors were contacted to obtain unpublished data at least 4 times in a one month period.

2.4. Outcomes

The primary outcomes were the serum levels of inflammatory cytokines and parameters in frail vs. pre-frail and robust (as separate entities) or vs. pre-frail/robust (as only one group). For incident frailty, the odds ratios (ORs) adjusted for the highest number of covariates available, were considered to assess the association between serum inflammatory parameters and frailty and considered as secondary outcome of our work.

2.5. Assessment of study quality

Study quality was assessed by two investigators (PS, PL), whilst a third reviewer was available for mediation (NV). For cross-sectional and longitudinal studies, the Newcastle-Ottawa Scale (NOS) (Wells et al., 2012) was used to assess study quality. The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome (Wells et al., 2012).

2.6. Statistical analysis

Analyses were performed by two independent investigators (NV, EC) using Comprehensive Meta-Analysis (CMA) 3 (http://www.meta-analysis.com). All cytokines were meta-analyzed when ≥3 studies contributed data.

In primary analyses, standardized mean differences (SMDs) and 95% confidence intervals (CI) were calculated. In the secondary analyses, the most adjusted pooled HRs were calculated for longitudinal analyses. When combining studies, the random effects model was used to account for anticipated heterogeneity (DerSimonian and Laird, 1986).

Heterogeneity was measured using the chi-squared and I-squared statistics, assuming that a $p \leq 0.10$ for the former and a value ≥50% for the latter indicated a significant heterogeneity (Higgins and Thompson, 2002).

Given significant heterogeneity, a meta-regression analysis was performed using differences in mean age, body mass index (BMI) and percentage of females among groups (frail, pre-frail, robust) as moderators. Moreover, a sensitivity analysis was conducted stratified by continent in which the study was performed (North America, Asia, Europe), setting (community-dwelling vs. hospital), and definition of frailty (Fried's criteria vs. other definitions).

Publication bias was assessed by visually inspecting funnel plots and using the Begg-Mazumdar Kendall tau (Begg and Mazumdar, 1994) and the Egger bias test (Egger et al., 1997). To account for publication bias, we used the trim-and-fill method, based on the assumption that the effect sizes of all the studies are normally distributed around the center of a funnel plot; in the event of asymmetries, it adjusts for the potential effect of unpublished studies (Egger et al., 1997). Finally, the fail safe number of negative studies that would be required to nullify (i.e. make $p > 0.05$) the effect size was calculated (Rosenthal, 1979).

3. Results

The search identified 1856 non-duplicated potentially eligible studies. After excluding papers following a review of titles and abstracts (mainly being reviews or not related to the association between frailty and inflammation, full details summarized in Supplementary Fig. 1), 66 full-text articles were examined, and 35 studies (32 cross-sectional (Addison et al., 2014; Almeida et al., 2012; Arts et al., 2015; Barzilay et al., 2007; Brouwers et al., 2015; Carcaillon et al., 2012; Chao et al., 2015; Collerton et al., 2012; Comptè et al., 2013; Darvin et al., 2014; Fontana et al., 2013; Gale et al., 2013; Hubbard et al., 2009; Hwang et al., 2015; Kalyani et al., 2012; Lai et al., 2014; Leng et al., 2011, 2007, 2004a,b; Liu et al., 2016; Piggott et al., 2015; Pustavoitau et al., 2016; Qu et al., 2009; Rønning et al., 2010; Saum et al., 2015; Sergi et al., 2015; Serviddio et al., 2009; Singer et al., 2015; Tsai et al., 2013; Walston et al., 2002; Wu et al., 2009) and 3 longitudinal (Baylis et al., 2013; Puts et al., 2005; Reiner et al., 2009)) were included in our meta-analysis (Supplementary Fig. 1).

3.1. Study and patient characteristics

Study and patient characteristics of cross-sectional studies are summarized in Supplementary Table 1.

The 32 cross-sectional studies (Addison et al., 2014; Almeida et al., 2012; Arts et al., 2015; Barzilay et al., 2007; Brouwers et al., 2015; Carcaillon et al., 2012; Chao et al., 2015; Collerton et al., 2012; Comptè et al., 2013; Darvin et al., 2014; Fontana et al., 2013; Gale et al., 2013; Hubbard et al., 2009; Hwang et al., 2015; Kalyani et al., 2012; Lai et al., 2014; Leng et al., 2011, 2007, 2004a,b; Liu et al., 2016; Piggott et al., 2015; Pustavoitau et al., 2016; Qu et al., 2009; Rønning et al., 2010; Saum et al., 2015; Sergi et al., 2015; Serviddio et al., 2009; Singer et al., 2015; Tsai et al., 2013; Wu et al., 2009) included a total of 23,910 older participants with a mean age of 75.2 ± 6.1 years.

Overall, there were 3332 (=13.9%) frail, 11,483 pre-frail (=48.0%) and 8532 robust subjects, while 563 additional participants were classified as pre-frail/robust.

All of the included studies used a modified version of Fried et al. (2001) definition for frailty, except for five defined by Frail Scale, Balducci Score, Modified Physical Performance Test Score, Identification of Seniors At Risk, MPI (Addison et al., 2014; Brouwers et al., 2015; Chao et al., 2015; Comptè et al., 2013; Fontana et al., 2013).

The majority of the studies were conducted among community-dwellers (22 studies; = 69%) and in North America (n = 14), followed by Europe (n = 11), Asia (n = 6) and Oceania (n = 1) (Supplementary Table 1). The quality of the studies, assessed through NOS, was gen-

erally good with a median = 7 (range: 4–9) (Supplementary Table 1).

Frail participants were older (mean age: 78.1 years), more frequently females (=61.8%) and with higher BMI (=26.8 kg/m^2) than pre-frail (age: 75.4 years; % of females: 58.9; BMI: 26.4 kg/m^2), robust (age: 72.8 years; % of females: 54.6; BMI: 26.3 kg/m^2) or pre-frail/robust (age: 74.8 years; % of females: 58.9; BMI: 25.8 kg/m^2) participants (Supplementary Table 1).

3.2. Cross-sectional meta-analysis findings

As reported in Table 1, 13 studies (Barzilay et al., 2007; Carcaillon et al., 2012; Collerton et al., 2012; Fontana et al., 2013; Hubbard et al., 2009; Hwang et al., 2015; Lai et al., 2014; Liu et al., 2016; Rønning et al., 2010; Saum et al., 2015; Tsai et al., 2013; Walston et al., 2002; Wu et al., 2009) reported that both frail (SMD = 1.00, 95%CI: 0.40–1.61, p < 0.0001; I^2 = 98%) and pre-frail (SMD = 0.33, 95%CI: 0.04–0.62, p = 0.03; I^2 = 98%) participants had significantly higher serum levels of CRP. The fail safe number of studies (i.e., the number of negative studies required to nullify our result >0.05) was very high for each of these analyses (see Table 1). Similar findings emerged when comparing frail vs. pre-frail/robust subjects in 4 studies (Almeida et al., 2012; Arts et al., 2015; Comptè et al., 2013; Gale et al., 2013) (SMD = 0.25, 95%CI: 0.02–−0.49, p = 0.04; I^2 = 81%).

Frailty (SMD = 1.12, 95%CI: 0.27–2.13, p = 0.01; I^2 = 99%) and pre-frailty (SMD = 0.56, 95%CI: 0.00–1.11, p = 0.05; I^2 = 99%) were associated with higher serum levels of IL-6 versus robust participants. The fail safe number of studies was 1650 and 1014 for the frailty and pre-frailty analyses, respectively.

Similar results were evident regarding white blood cells and fibrinogen levels, while no differences emerged for TNF-alpha (Table 1).

3.3. Meta-regression and sensitivity analyses

Since the differences in inflammatory parameters between frailty, pre-frailty and robustness were characterized by a high heterogeneity ($I^2 \geq 50\%$, p < 0.05), where a sufficient number of studies were available (at least 4 for each outcome), we ran a meta-regression analysis to seek potential moderators.

As shown in Supplementary 2, very few moderators appeared to explain the heterogeneity present in our analyses. Differences in age between the frail and robust samples moderated the results in the comparison between frail vs. pre-frail/robust regarding CRP (beta = −0.08; 95%CI: −0.11 to −0.04, p = 0.0003, R^2 = 1.00) and IL-6 (beta = −0.24; 95%CI: −0.40 to −0.08, p = 0.004, R^2 = 0.82), while higher differences in BMI between frail (beta = 0.97; 95%CI: 0.46–1.49, p = 0.002, R^2 = 0.55) or pre-frail (beta = 0.76; 95%CI: 0.18–1.35, p = 0.01, R^2 = 0.39) vs. robust participants moderated the results regarding CRP (Supplementary Table 2).

Supplementary Table 3 shows the results of cross-sectional studies according to some strata, namely country in which the study was performed, the setting and the definition of frailty. Overall, these moderators seem not to significantly affect our findings. In particular, we found that frailty and pre-frailty were associated with significantly elevated CRP and IL-6 levels across all geographical settings and among community and institutionalized participants (see Supplementary Table 3).

3.4. Longitudinal meta-analysis findings

Three studies (Baylis et al., 2013; Puts et al., 2005; Reiner et al., 2009) followed-up 3402 older participants without frailty at baseline for a median of 3 years (range: 3–10) (Supplementary Table 4).

Table 1
Meta-analysis of studies comparing frail vs. pre-frail or robust older participants with publication bias assessment.

Analysis	Number of studies	Number participants		Meta-analysis			Heterogeneity	Publication bias		Classic fail safe N
		1st group	2nd group	SMD	95% CI	P value	I^2	Egger bias & p value	Trim and fill (95% CI)	
C reactive protein										
Frail vs. robust	13	1698	6757	**1.00**	**0.40**	**1.61**	**98**	2.65; 0.68	1.08 (0.50–1.67)	2572
Pre-frail vs. robust	13	8568	6757	**0.33**	**0.04**	**0.62**	98	−0.17; 0.97	0.42 (0.16–0.68)	1213
Frail vs. pre-frail/robust	4	548	5794	**0.25**	**0.02**	**0.49**	81	0.97; 0.80	Unchanged	20
IL-6										
Frail vs. robust	12	1057	2392	**1.12**	**0.27**	**2.13**	**99**	3.04; 0.63	1.68 (0.86–2.51)	1650
Pre-frail vs. robust	12	4467	2392	**0.56**	**0.00**	**1.11**	99	−0.84; 0.86	0.69 (0.19–1.19)	1014
Frail vs. pre-frail/robust	6	249	600	0.56	−0.27	1.40	95	−1.22; 0.78	0.71 (−0.05; 1.48)	79
Tumor Necrosis factor-alpha										
Frail vs. robust	4	232	226	0.42	−0.29	1.12	91	7.35; 0.19	Unchanged	4
Pre-frail vs. robust	4	509	226	0.20	−0.40	0.80	91	5.68; 0.16	Unchanged	0
Frail vs. pre-frail/robust	3	67	51	0.22	−0.17	0.56	0	−0.40; 0.79	Unchanged	0
White blood cells										
Frail vs. robust	6	953	2321	**0.45**	**0.30**	**0.59**	**55**	2.37; 0.07	0.33 (0.18–0.48)	140
Pre-frail vs. robust	6	4049	2321	**0.27**	**0.13**	**0.41**	76	2.46; 0.08	0.36 (0.15–0.56)	76
Frail vs. pre-frail/robust	Only one study									
Fibrinogen										
Frail vs. robust	5	858	4329	**0.54**	**0.30**	**0.79**	**86**	3.82; 0.09	0.34 (0.06–0.63)	149
Pre-frail vs. robust	5	5674	4329	**0.27**	**0.13**	**0.40**	86	3.03; 0.19	0.21 (0.01–0.32)	113
Frail vs. pre-frail/robust	Only one study									

The bold values are to highlight the significant differences between groups.
Abbreviations:, CI = confidence interval, SMD = standardized mean difference.

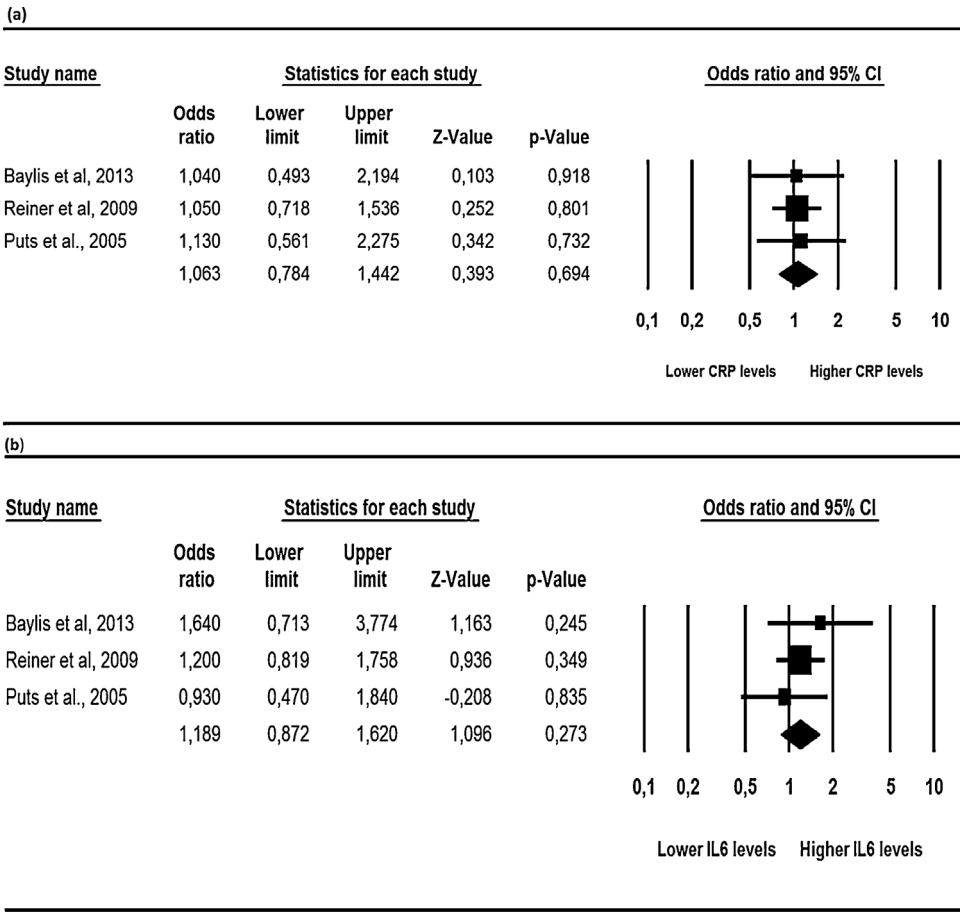

Fig. 1. Relationship between serum C-reactive protein levels (a) and interleukin 6 (b) at baseline and incident frailty, adjusted for potential confounders.

After adjusting for a median of 9 potential confounders (range: 7–10), both higher serum CRP (OR = 1.06, 95%CI: 0.78–1.44, p = 0.69, $I^2$0%; Fig. 1a) and IL-6 (OR = 1.19, 95%CI: 0.87–1.62, p = 0.27, $I^2$0%; Fig. 1b) levels were not associated with higher risk of frailty.

3.5. Publication bias

Judging from a visual inspection of funnel plots and using Egger's test (Table 1 for cross-sectional studies), no publication bias was evident for all the outcomes included. A similar absence of publication bias was present for longitudinal studies, although limited by the number of studies included.

4. Discussion

In this meta-analysis including 32 cross-sectional studies and 23,910 older subjects, we observed that frailty and pre-frailty were associated with significantly higher serum inflammatory parameters compared to robust participants. In particular, we found a large increase in CRP and IL-6 in frail and pre-frail participants versus robust participants, with very high fail safe number of studies required to nullify these results. The elevated CRP and IL-6 were consistent across geographical regions and both in community and hospital settings. We also found evidence of elevated white bloods cells and fibrinogen. On the contrary, three large prospective studies failed to find any association between higher inflammatory levels at baseline and incident frailty. Meta-regression analyses of the cross-sectional data suggest that age and BMI moderate the relationship between CRP and frailty.

The relationship between inflammation and frailty is complex since both linearly increase with advancing old age. Both higher inflammatory levels and frailty are associated with several negative outcomes in the elderly, like higher mortality, hospitalization rate and co-morbidity onset (Piggott et al., 2015; Sergi et al., 2015; Zunszain et al., 2013). In cross-sectional studies, the association of frailty with higher inflammation appears to be consistent since both frail and pre-frail participants showed significant higher serum levels of CRP, TNF-a, IL-6, white blood cells and fibrinogen. Several reasons could explain these results. First, frail and pre-frail participants have a higher presence of concomitant factors like disability, medical conditions that could increase the inflammatory parameters. Second, as confirmed by our analyses, frail and pre-frail people (particularly if community-dwelling) are generally more obese than robust participants, and obesity significantly increases inflammatory parameters (Greenberg and Obin, 2006; Solmi et al., 2015; Veronese et al., 2015). This hypothesis is also in line with the increase in adiposity observed in frail subjects that seems to affect also muscular mass (Addison et al., 2014) and indirectly confirmed by our meta-regression analysis showing that higher differences in BMI between frail or pre-frail vs. robust participants moderated the results regarding serum CRP concentrations. Finally, frail people seem to have a significant reduction in innate immune system, T-cell activity, antibodies production and increase in mitochondrial activity with an increase in oxidative stress products, ultimately leading to an increase in serum inflammatory levels (Hubbard and Woodhouse, 2010; Li et al., 2011).

Conversely, the analyses from our longitudinal studies did not show any association between higher inflammatory levels and the

onset of frailty. The lack of relationship might be due to the paucity of data, however, it may well also indicate that these inflammatory markers are not associated with a predisposition for developing frailty and may arise once frailty has set int. Another hypothesis is that the longitudinal studies included in our meta-analysis included a median of 9 baseline potential confounders. Therefore, an over-adjustment of the analyses could not to be excluded. The absence of an univocal operational definition for frailty, in fact, makes the development of measurable biomarkers particularly important (Calvani et al., 2015) and if higher inflammatory parameters are able to predict the onset of frailty could be of importance since they are largely diffused worldwide and since higher inflammatory parameters probably contribute to transitions from frailty to disability and other negative outcomes (Zaslavsky et al., 2013). A possible hypothesis for this lack of association is that frail people are very sensitive to acute and sub-acute diseases that might increase inflammatory parameters during follow-up period and none of the studies included adjusted their analyses for inherent changes in these markers. Clearly, future studies including these adjustments are needed to better investigate the potential role of inflammatory parameters in predicting frailty in the elderly.

The meta-regression analyses identified some characteristics of frail and pre-frail participants compared to robust subjects could explain the differences in inflammatory parameters seen. In particular, differences in age and BMI moderated the results in the comparison between frail vs. pre-frail/robust regarding CRP and IL-6 suggesting an important role of these factors in the higher inflammatory levels found in these subjects compared to robust ones. On the contrary, the definition of frailty did not affect our findings suggest that, independently from the definition used, frail people are characterized by a metabolic signature in which inflammation plays a relevant role (Fontana et al., 2013).

The findings of our study should be interpreted within its limitations. First, we encountered moderate-high heterogeneity in most of the cross-sectional analyses. Whilst the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines state heterogeneity is to be expected when analyzing observational data, we were only partially able to explain the heterogeneity with meta regression analysis. Second, almost all the studies used the criteria proposed by Fried et al., but this definition includes only physical frailty and does not consider other aspects (for instance cognitive status), which is of relevance in frailty (Zaslavsky et al., 2013). The focus on physical frailty is not suitable for people with advance cognitive decline (e.g. dementia) who may also be highly susceptible to frailty. Therefore, future research is also required to understand frailty (considering cognitive status) and inflammation among people with dementia. Moreover, the frailty phenotype did not allow to a better understanding of the underlying contributing factors to frailty and inflammation. Third, the categorization of people as robust/pre-frail/frail other factors (e.g. differences in comorbidities) may explain some of the relationship between physical frailty and inflammation. Therefore, future studies using other definitions of frailty should attempt to match up frail/pre frail and robust participants and account for between group differences in important comorbidities/factors which may also influence inflammation. Fourth, all the studies investigating frailty according to the definition of Fried et al. and did not use the original versions and instead adapted the frailty criteria which can influence the quality of the composite score and potentially introduce bias (Theou et al., 2015). Agreement between modified criteria with the primary frailty phenotype, in fact, is generally low-moderate. However, the impact of this on our results is unclear. Finally, only three longitudinal studies were eligible, with a lack of clarity concerning the results. Therefore, future longitudinal research is required to disentangle the directionality of the inflammation and frailty relationships we observed in our comprehensive cross sectional analyses. Nonetheless, our meta-analysis is a first and included a large number of studies included and inflammatory outcomes. The data from our cross sectional results were also free from publication bias and the results indicating greatly increased levels of CRP and IL-6 had very large fail safe number of studies (both >1000).

In conclusion, frailty and pre-frailty are associated with higher inflammatory parameters levels, in particular CRP and IL-6. However, longitudinal studies did not confirm these findings, suggesting that other studies are needed to better understand if these inflammatory markers could be used as potential biomarkers of frailty in the elderly.

Conflict of interest

None.

Financial disclosure

Soysal, Stubbs, Lucato, Luchini, Solmi, Peluso, Sergi, Isik, Manzato, Maggi, Maggio, Prina, Cosco, Wu, Veronese have nothing to disclose.

Acknowledgments

We thank Carmen Martin-Ruiz, M.D., Biomarkers Lab manager, Ageing Research Laboratories, Institute of Neuroscience and Newcastle University Institute for Ageing; Jose Antonio Carnicero, Toledo Study for Healthy Ageing; Nathalie Compté M.D., Institute for Medical Immunology (IMI), Universiteí Libre de Bruxelles, Charleroi, Belgium; Aliaksei Pustavoitau M.D., Department of Anesthesiology and Critical Care Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA; Kai-Uwe Saum M.D., Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Germany; An-Chun Hwang M.D., Center for Geriatrics and Gerontology, Taipei Veterans General Hospital; Sigrid Hatse, Ph.D. Multidisciplinary Breast Center (MBC), Laboratory of Experimental Oncology/Department of Oncology for sending us their data.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arr.2016.08.006.

References

Addison, O., Drummond, M.J., LaStayo, P.C., Dibble, L.E., Wende, A.R., McClain, D.A., Marcus, R.L., 2014. Intramuscular fat and inflammation differ in older adults: the impact of frailty and inactivity. J. Nutr. Health Aging 18, 532–538, http://dx.doi.org/10.1007/s12603-014-0019-1.

Almeida, O.P., Norman, P.E., Van Bockxmeer, F.M., Hankey, G.J., Flicker, L., 2012. CRP 1846G > A polymorphism increases risk of frailty. Maturitas 71, 261–266, http://dx.doi.org/10.1016/j.maturitas.2011.11.022.

Arts, M.H.L., Collard, R.M., Comijs, H.C., Naudé, P.J.W., Risselada, R., Naarding, P., Oude Voshaar, R.C., 2015. Relationship between physical frailty and low-grade inflammation in late-life depression. J. Am. Geriatr. Soc. 63, 1652–1657, http://dx.doi.org/10.1111/jgs.13528.

Barzilay, J.I., Blaum, C., Moore, T., Xue, Q.L., Hirsch, C.H., Walston, J.D., Fried, L.P., 2007. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. Arch. Intern. Med. 167, 635–641, http://dx.doi.org/10.1001/archinte.167.7.635.

Baylis, D., Bartlett, D.B., Syddall, H.E., Ntani, G., Gale, C.R., Cooper, C., Lord, J.M., Sayer, A.A., 2013. Immune-endocrine biomarkers as predictors of frailty and mortality: a 10-year longitudinal study in community-dwelling older people. Age 35, 963–971, http://dx.doi.org/10.1007/s11357-012-9396-8.

Begg, C.B., Mazumdar, M., 1994. Operating characteristics of a rank correlation test for publication bias. Biometrics 50, 1088–1101, http://dx.doi.org/10.2307/2533446.

Brouwers, B., Dalmasso, B., Hatse, S., Laenen, A., Kenis, C., Swerts, E., Neven, P., Smeets, A., Schöffski, P., Wildiers, H., 2015. Biological ageing and frailty markers in breast cancer patients. Aging (Milano) 7, 319–333.

Calvani, R., Marini, F., Cesari, M., Tosato, M., Anker, S.D., Von Haehling, S., Miller, R.R., Bernabei, R., Landi, F., Marzetti, E., 2015. Biomarkers for physical frailty and sarcopenia: state of the science and future developments. J. Cachexia Sarcopenia Muscle 6, 278–286, http://dx.doi.org/10.1002/jcsm.12051.

Carcaillon, L., García-García, F.J., Tresguerres, J.A.F., Gutiérrez Avila, G., Kireev, R., Rodríguez-Mãnas, L., 2012. Higher levels of endogenous estradiol are associated with frailty in postmenopausal women from the toledo study for healthy aging. J. Clin. Endocrinol. Metab. 97, 2898–2906, http://dx.doi.org/10.1210/jc.2012-1271.

Chao, C. Ter, Hsu, Y.H., Chang, P.Y., He, Y.T., Ueng, R.S., Lai, C.F., Chiang, C.K., Huang, J.W., Huang, S.J., 2015. Simple self-report FRAIL scale might be more closely associated with dialysis complications than other frailty screening instruments in rural chronic dialysis patients. Nephrology 20, 321–328, http://dx.doi.org/10.1111/nep.12401.

Chen, X., Mao, G., Leng, S.X., 2014. Frailty syndrome: an overview. Clin. Interv. Aging, http://dx.doi.org/10.2147/cia.s45300.

Clegg, A., Young, J., Iliffe, S., Rikkert, M.O., Rockwood, K., 2013. Frailty in elderly people. Lancet 381, 752–762, http://dx.doi.org/10.1016/S0140-6736(12)62167-9.

Collerton, J., Martin-Ruiz, C., Davies, K., Hilkens, C.M., Isaacs, J., Kolenda, C., Parker, C., Dunn, M., Catt, M., Jagger, C., von Zglinicki, T., Kirkwood, T.B.L., 2012. Frailty and the role of inflammation, immunosenescence and cellular ageing in the very old: cross-sectional findings from the newcastle 85+ study. Mech. Ageing Dev. 133, 456–466, http://dx.doi.org/10.1016/j.mad.2012.05.005.

Comptè, N., Zouaoui Boudjeltia, K., Vanhaeverbeek, M., De Breucker, S., Tassignon, J., Trelcat, A., Pepersack, T., Goriely, S., 2013. Frailty in old age is associated with decreased interleukin-12/23 production in response to Toll-like receptor ligation. PLoS One 8, 4–14, http://dx.doi.org/10.1371/journal.pone.0065325.

Darvin, K., Randolph, A., Ovalles, S., Halade, D., Breeding, L., Richardson, A., Espinoza, S.E., 2014. Plasma protein biomarkers of the geriatric syndrome of frailty. J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 69A, 182–186, http://dx.doi.org/10.1093/gerona/glt183.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7, 177–188, http://dx.doi.org/10.1016/0197-2456(86)90046-2.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clin. Res. Ed.) 315, 629–634, http://dx.doi.org/10.1136/bmj.316.7129.469.

Fontana, L., Addante, F., Copetti, M., Paroni, G., Fontana, A., Sancarlo, D., Pellegrini, F., Ferrucci, L., Pilotto, A., 2013. Identification of a metabolic signature for multidimensional impairment and mortality risk in hospitalized older patients. Aging Cell 12, 459–466, http://dx.doi.org/10.1111/acel.12068.

Fried, L.P., Tangen, C.M., Walston, J., Newman, A.B., Hirsch, C., Gottdiener, J., Seeman, T., Tracy, R., Kop, W.J., Burke, G., McBurnie, M.A., 2001. Frailty in older adults: evidence for a phenotype. J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 56, M146–56.

Gale, C.R., Baylis, D., Cooper, C., Sayer, A.A., 2013. Inflammatory markers and incident frailty in men and women: the english longitudinal study of ageing. Age 35, 2493–2501, http://dx.doi.org/10.1007/s11357-013-9528-9.

Greenberg, A.S., Obin, M.S., 2006. Obesity and the role of adipose tissue in inflammation and metabolism. Am. J. Clin. Nutr. 83, 461S–465.

Higgins, J.P.T., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. Stat. Med. 21, 1539–1558, http://dx.doi.org/10.1002/sim.1186.

Hubbard, R.E., Woodhouse, K.W., 2010. Frailty, inflammation and the elderly. Biogerontology 11, 635–641, http://dx.doi.org/10.1007/s10522-010-9292-5.

Hubbard, R.E., O'Mahony, M.S., Savva, G.M., Calver, B.L., Woodhouse, K.W., 2009. Inflammation and frailty measures in older people. J. Cell. Mol. Med. 13, 3103–3109, http://dx.doi.org/10.1111/j.1582-4934.2009.00733.x.

Hwang, A.-C., Liu, L.-K., Lee, W.-J., Chen, L.-Y., Peng, L.-N., Lin, M.-H., Chen, L.-K., 2015. Association of frailty and cardiometabolic risk among community-dwelling middle-aged and older people: results from the I-Lan longitudinal aging study. Rejuvenation Res. 18, 564–572, http://dx.doi.org/10.1089/rej.2015.1699.

Kalyani, R.R., Varadhan, R., Weiss, C.O., 2012. Frailty status and altered dynamics of circulating energy. J. Nutr. Health Aging, 16.

Lai, H.Y., Chang, H.T., Lee, Y.L., Hwang, S.J., 2014. Association between inflammatory markers and frailty in institutionalized older men. Maturitas 79, 329–333, http://dx.doi.org/10.1016/j.maturitas.2014.07.014.

Lang, P.O., Michel, J.P., Zekry, D., 2009. Frailty syndrome: a transitional state in a dynamic process. Gerontology, http://dx.doi.org/10.1159/000211949.

Leng, S.X., Cappola, A.R., Andersen, R.E., Blackman, M.R., Koenig, K., Blair, M., Walston, J.D., 2004a. Serum levels of insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. Aging Clin. Exp. Res. 16, 153–157.

Leng, S.X., Yang, H., Walston, J.D., 2004b. Decreased cell proliferation and altered cytokine production in frail older adults. Aging Clin. Exp. Res. 16, 249–252.

Leng, S.X., Xue, Q.L., Tian, J., Walston, J.D., Fried, L.P., 2007. Inflammation and frailty in older women. J. Am. Geriatr. Soc. 55, 864–871, http://dx.doi.org/10.1111/j.1532-5415.2007.01186.x.

Leng, S.X., Tian, X., Matteini, A., Li, H., Hughes, J., Jain, A., Walston, J.D., Fedarko, N.S., 2011. Il-6-independent association of elevated serum neopterin levels with prevalent frailty in community-dwelling older adults. Age Ageing 40, 475–481, http://dx.doi.org/10.1093/ageing/afr047.

Li, H., Manwani, B., Leng, S.X., 2011. Frailty, inflammation, and immunity. Aging Dis. 2, 466–473.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P.A., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 6, e1000100, http://dx.doi.org/10.1371/journal.pmed.1000100.

Liu, C.K., Lyass, A., Larson, M.G., Massaro, J.M., Wang, N., D'Agostino, R.B., Benjamin, E.J., Murabito, J.M., 2016. Biomarkers of oxidative stress are associated with frailty: the Framingham Offspring Study. Age (Dordr. Neth.) 38, 1, http://dx.doi.org/10.1007/s11357-015-9864-z.

Newman, A.B., Gottdiener, J.S., Mcburnie, M.A., Hirsch, C.H., Kop, W.J., Tracy, R., Walston, J.D., Fried, L.P., 2001. Associations of subclinical cardiovascular disease with frailty. J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 56, M158–66.

Piggott, D.A., Varadhan, R., Mehta, S.H., Brown, T.T., Li, H., Walston, J.D., Leng, S.X., Kirk, G.D., 2015. Frailty, inflammation, and mortality among persons aging with HIV infection and injection drug use. J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 70, 1542–1547, http://dx.doi.org/10.1093/gerona/glv107.

Pustavoitau, A., Barodka, V., Sharpless, N.E., Torrice, C., Nyhan, D., Berkowitz, D.E., Shah, A.S., Bandeen Roche, K.J., Walston, J.D., 2016. Role of senescence marker p16INK4a measured in peripheral blood T-lymphocytes in predicting length of hospital stay after coronary artery bypass surgery in older adults. Exp. Gerontol. 74, 29–36, http://dx.doi.org/10.1016/j.exger.2015.12.003.

Puts, M.T.E., Visser, M., Twisk, J.W.R., Deeg, D.J.H., Lips, P., 2005. Endocrine and inflammatory markers as predictors of frailty. Clin. Endocrinol. (Oxf.) 63, 403–411, http://dx.doi.org/10.1111/j1365-2265.2005.02355. x.

Qu, T., Yang, H., Walston, J.D., Fedarko, N.S., Leng, S.X., 2009. Upregulated monocytic expression of CXC chemokine ligand 10 (CXCL-10) and its relationship with serum interleukin-6 levels in the syndrome of frailty. Cytokine 46, 319–324, http://dx.doi.org/10.1016/j.cyto.2009.02.015.

Rønning, B., Wyller, T.B., Seljeflot, I., Jordhøy, M.S., Skovlund, E., Nesbakken, A., Kristjansson, S.R., 2010. Frailty measures, inflammatory biomarkers and post-operative complications in older surgical patients. Age Ageing 39, 758–761, http://dx.doi.org/10.1093/ageing/afq123.

Reiner, A.P., Aragaki, A.K., Gray, S.L., Wactawski-Wende, J., Cauley, J.A., Cochrane, B.B., Kooperberg, C.L., Woods, N.F., LaCroix, A.Z., 2009. Inflammation and thrombosis biomarkers and incident frailty in postmenopausal women. Am. J. Med. 122, 947–954, http://dx.doi.org/10.1016/j.amjmed.2009.04.016.

Rosenthal, R., 1979. The file drawer problem and tolerance for null results. Psychol. Bull. 86, 638–641, http://dx.doi.org/10.1037/0033-2909.86.3.638.

Saum, K.U., Dieffenbach, A.K., Jansen, E.H.J.M., Schöttker, B., Holleczek, B., Hauer, K., Brenner, H., 2015. Association between oxidative stress and frailty in an elderly German population: results from the esther cohort study. Gerontology 61, 407–415, http://dx.doi.org/10.1159/000380881.

Sergi, G., Veronese, N., Fontana, L., De Rui, M., Bolzetta, F., Zambon, S., Corti, M.-C., Baggio, G., Toffanello, E.D., Crepaldi, G., Perissinotto, E., Manzato, E., 2015. Pre-frailty and risk of cardiovascular disease in elderly men and women: the pro.v.a. study. J. Am. Coll. Cardiol. 65, 976–983, http://dx.doi.org/10.1016/j.jacc.2014.12.040.

Serviddio, G., Romano, A.D., Greco, A., Rollo, T., Bellanti, F., Altomare, E., Vendemiale, G., 2009. Frailty syndrome is associated with altered circulating redox balance and increased markers of oxidative stress. Int. J. Immunopathol. Pharmacol. 22, 819–827.

Singer, J.P., Diamond, J.M., Gries, C.J., McDonnough, J., Blanc, P.D., Shah, R., Dean, M.Y., Hersh, B., Wolters, P.J., Tokman, S., Arcasoy, S.M., Ramphal, K., Greenland, J.R., Smith, N., Heffernan, P., Shah, L., Shrestha, P., Golden, J.A., Blumenthal, N.P., Huang, D., Sonett, J., Hays, S., Oyster, M., Katz, P.P., Robbins, H., Brown, M., Leard, L.E., Kukreja, J., Bacchetta, M., Bush, E., D'Ovidio, F., Rushefski, M., Raza, K., Christie, J.D., Lederer, D.J., 2015. Frailty phenotypes, disability, and outcomes in adult candidates for lung transplantation. Am. J. Respir. Crit. Care Med. 192, 1325–1334, http://dx.doi.org/10.1164/rccm.201506-1150OC.

Solmi, M., Veronese, N., Favaro, A., Santonastaso, P., Manzato, E., Sergi, G., Correll, C.U., 2015. Inflammatory cytokines and anorexia nervosa: a meta-analysis of cross-sectional and longitudinal studies. Psychoneuroendocrinology 51, 237–252, http://dx.doi.org/10.1016/j.psyneuen.2014.09.031.

Theou, O., Cann, L., Blodgett, J., Wallace, L.M.K., Brothers, T.D., Rockwood, K., 2015. Modifications to the frailty phenotype criteria: systematic review of the current literature and investigation of 262 frailty phenotypes in the survey of health, ageing, and retirement in Europe. Ageing Res. Rev., http://dx.doi.org/10.1016/j.arr.2015.04.001.

Tsai, J.S., Wu, C.H., Chen, S.C., Huang, K.C., Chen, C.Y., Chang, C.I., Chuang, L.M., Chen, C.Y., 2013. Plasma adiponectin levels correlate positively with an increasing number of components of frailty in male elders. PLoS One 8, 1–8, http://dx.doi.org/10.1371/journal.pone.0056250.

von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., STROBE initiative, 2008. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guildelines for reporting observational studies. J. Clin. Epidemiol. 61, 344–349, http://dx.doi.org/10.1016/j.jclinepi.2007.11.008.

Veronese, N., Cereda, E., Solmi, M., Fowler, S.A., Manzato, E., Maggi, S., Manu, P., Abe, E., Hayashi, K., Allard, J.P., Arendt, B.M., Beck, A., Chan, M., Audrey, Y.J.P., Lin, W.-Y., Hsu, H.-S., Lin, C.-C., Diekmann, R., Kimyagarov, S., Miller, M., Cameron, I.D., Pitkälä, K.H., Lee, J., Woo, J., Nakamura, K., Smiley, D., Umpierrez, G., Rondanelli, M., Sund-Levander, M., Valentini, L., Schindler, K., Törmä, J.,

Volpato, S., Zuliani, G., Wong, M., Lok, K., Kane, J.M., Sergi, G., Correll, C.U., 2015. Inverse relationship between body mass index and mortality in older nursing home residents: a meta-analysis of 19,538 elderly subjects. Obes. Rev., http://dx.doi.org/10.1111/obr.12309.

Walston, J., McBurnie, M.A., Newman, A., Tracy, R.P., Kop, W.J., Hirsch, C.H., Gottdiener, J., Fried, L.P., 2002. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch. Intern. Med. 162, 2333–2341, http://dx.doi.org/10.1001/archinte.162.20.2333.

Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P., 2012. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality If Nonrandomized Studies in Meta-analyses., http://dx.doi.org/10.2307/632432, Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Wu, I.C., Shiesh, S.C., Kuo, P.H., Lin, X.Z., 2009. High oxidative stress is correlated with frailty in elderly Chinese. J. Am. Geriatr. Soc. 57, 1666–1671, http://dx.doi.org/10.1111/j.1532-5415.2009.02392.x.

Yao, X., Li, H., Leng, S.X., 2011. Inflammation and immune system alterations in frailty. Clin. Geriatr. Med., http://dx.doi.org/10.1016/j.cger.2010.08.002.

Zaslavsky, O., Cochrane, B.B., Thompson, H.J., Woods, N.F., Herting, J.R., LaCroix, A., 2013. Frailty: a review of the first decade of research. Biol. Res. Nurs. 15, 422–432, http://dx.doi.org/10.1177/1099800412462866.

Zunszain, P.A., Hepgul, N., Pariante, C.M., 2013. Inflammation and depression. Curr. Top. Behav. Neurosci. 14, 135–151, http://dx.doi.org/10.1007/7854_2012_211.