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Review

Evidence-based nutritional and pharmacological interventions targeting chronic low-grade inflammation in middle-age and older adults: A systematic review and meta-analysis

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ABSTRACT

Growing evidence suggests chronic low-grade inflammation (LGI) as a possible mechanism underlying the aging process. Some biological and pharmaceutical compounds may reduce systemic inflammation and potentially avert functional decline occurring with aging. The aim of the present meta-analysis was to examine the association of pre-selected interventions on two established biomarkers of inflammation, interleukin-6 (IL-6), and C-reactive protein (CRP) in middle-age and older adults with chronic LGI.

We reviewed the literature on potential anti-inflammatory compounds, selecting them based on safety, tolerability, acceptability, innovation, affordability, and evidence from randomized controlled trials. Six compounds met all five inclusion criteria for our systematic review and meta-analysis: angiotensin II receptor blockers (ARBs), metformin, omega-3, probiotics, resveratrol and vitamin D. We searched in MEDLINE, PubMed and EMBASE database until January 2017. A total of 49 articles fulfilled the selection criteria. Effect size of each study and pooled effect size for each compound were measured by the standardized mean difference. I^2 was computed to measure heterogeneity of effects across studies.

The following compounds showed a significant small to large effect in reducing IL-6 levels: probiotics (−0.68 pg/ml), ARBs (−0.37 pg/ml) and omega-3 (−0.19 pg/ml). For CRP, a significant small to medium effect was observed with probiotics (−0.43 mg/L), ARBs (−0.2 mg/L), omega-3 (−0.17 mg/L) and metformin (−0.16 mg/L). Resveratrol and vitamin D were not associated with any significant reductions in either biomarker.

These results suggest that nutritional and pharmaceutical compounds can significantly reduce established biomarkers of systemic inflammation in middle-age and older adults. The findings should be interpreted with caution, however, due to the evidence of heterogeneity across the studies.

1. Introduction

Older age is often associated with a higher burden of comorbidities that lead to declines in physical and cognitive function and ultimately, disability and death (Marengoni et al., 2009). In recent years inflammation has been shown to contribute to most if not all chronic diseases typical of old age (Stepanova et al., 2015). Moreover, aging itself could result in immune system dysregulation leading to chronic

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low-grade inflammation (LGI) (Ferrucci et al., 2005). Growing evidence suggests chronic low level elevation of proinflammatory cytokines and chemokines, a process also defined as "inflammaging" specifically contributes to age-related decline in function and increases risk of morbidity and mortality (Franceschi and Campisi, 2014).

The origin of inflammaging currently remains unclear (Baylis et al., 2013; Fougere et al., 2017; Franceschi et al., 2000; Fulop et al., 2014). Although there is likely a genetic predisposition (Capurso et al., 2007), many other factors can contribute to the inflammatory process. Some identified exogenous triggers include smoking (Behnia et al., 2016), air pollution (Fougere et al., 2015), persistent infections (Derhovanessian et al., 2011; Oppermann et al., 2012) and overweight or obesity (Giugliano et al., 2006). Several endogenous factors also play a relevant role, including: overproduction of reactive oxygen species (ROS) (Zhang et al., 2016) and advanced glycation end-products (AGEs) (Yamagishi and Matsui, 2016), mitochondrial dysfunction (Lopez-Lluch et al., 2015), renin-angiotensin system (RAS) deregulation (Duprez, 2006), hormonal changes (Epel and Lithgow, 2014; Gubbels Bupp, 2015), visceral adiposity (Palmer and Kirkland, 2016), changes in the gut microbiota (Biagi et al., 2010) and accumulation of cell debris due to a defective autophagy (Franceschi et al., 2017).

In humans, two of the most well accepted markers of systemic inflammation are interleukin-6 (IL-6) and C-reactive protein (CRP) (Michaud et al., 2013). The levels of both biomarkers typically increase with aging (Singh and Newman, 2011; Wyczalkowska-Tomasik et al., 2016), which leads to an increased risk of morbidity and mortality in older adults (Alley et al., 2007; Ferrucci et al., 1999; Harris et al., 1999). Higher IL-6 levels have been associated with indicators of physical frailty such as slower walking speed, impaired muscle strength, and lower extremity performance (Cesari et al., 2004; Taaffe et al., 2000), and sarcopenia (Haddad et al., 2005) which are predictive of future disability in nondisabled older adults (Ferrucci et al., 1999). Moreover, in the Longitudinal Aging Study of Amsterdam, moderately elevated CRP levels (3–10 mg/L) were associated with 3-year incident frailty (Puts et al., 2005). Elevated levels of both IL-6 and CRP have also been related to a decline in cognitive function (Schram et al., 2007) and Alzheimer's disease (AD) (Akiyama et al., 2000).

The rise of IL-6 and CRP levels are mechanistically linked to the activation of pro-inflammatory transcription factors, including nuclear factor kappa B (NF-κB) (Maggio et al., 2006). A consistent body of evidence suggests NF-κB is an attractive target for anti-inflammatory therapies (Gupta et al., 2010). Thus, the inhibitors, at various levels, of NF-κB pathway could lead to a reduction of inflammatory biomarkers (such as IL-6 and CRP) and potentially avert or slow the functional decline that occurs with aging.

A recent review by Gupta et al. (2010), based on *in vitro* data, provided a comprehensive overview on potential compounds that can inhibit the NF-κB pathway, including natural and synthetic products, proteins, and peptides. Although there is a growing body of evidence to suggest many of these compounds can reduce established inflammatory biomarkers, to date, the findings have not been systematically examined in middle-age and older adults with chronic LGI. Thus, the goal of this review was to examine the state of evidence from relevant randomized controlled trials (RCTs) to identify the most promising biological and pharmacological compounds that reduce inflammation in middle-age and older adults with elevated circulating levels of IL-6 and/or CRP.

2. Methods

2.1. Search strategy and study selection

This systematic literature review and meta-analysis followed the requirements of the PRISMA statement (Moher et al., 2009). The review was registered in PROSPERO, the international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO; registration number: CRD42017059820)

Three study authors (C.C., R.T.M. and S.A.L.) independently conducted a systematic search of the databases MEDLINE, PubMed, and EMBASE (all years to January 31st 2017).

To initially identify the potential compounds, we considered the molecules listed in a recent review by Gupta et al. (2010), since this review provided, on a molecular base, a comprehensive overview of targets of NF-κB. Furthermore, to maximize the public health impact of our meta-analysis, we selected compounds based on four criteria: safety, tolerability and acceptability, innovation, and affordability. First, we evaluated compounds in terms of their safety record in the general population, risk of adverse events, and potential interactions with other drugs. Next, we took into account tolerability and acceptability, considering side effects that may reduce quality of life and adherence to the treatment. For our innovation criterion, we prioritized compounds that did not already have an indication for anti-inflammatory therapy (e.g., non-steroidal anti-inflammatory drugs, corticosteroids and interleukin (IL)-1 beta inhibitor were excluded). Next, we considered costs of specific compounds and the potential for individuals to take specific compounds on a regular basis. To be included in the present meta-analysis, compounds had to meet all four criteria listed above.

Once we identified potential compounds, we applied the fifth criterion which was to select compounds that had sufficient evidence from four or more RCTs conducted in middle-age and older adults with chronic LGI (indicated by either elevated IL-6 or CRP levels). After a preliminary search in the above-mentioned databases, we excluded compounds that had less than four eligible studies. Several compounds that met our initial criteria (e.g. curcumin, vitamin-B6, −C, −E, β-carotene, melatonin) were subsequently excluded due to lack of sufficient evidence from clinical trials in middle-age and older adults with chronic LGI. Table 1 reports the results of the selection process.

Six compounds met all five inclusion criteria and were included in our systematic review and meta-analysis: angiotensin II receptor blockers (ARBs), metformin, omega-3, probiotics, resveratrol, and vitamin D. Search terms included combinations of the following keywords: ("losartan" OR "candesartan" OR "valsartan" OR "irbesartan" OR "telmisartan" OR "olmesartan" OR "eprosartan" OR "azilsartan" OR "fimasartan" OR "metformin" OR "omega-3 fatty acids" OR "n-3 polyunsaturated fatty acid" OR "n-3 pufa" OR "probiotic" OR "resveratrol" OR "vitamin D" OR "cholecalciferol" OR "ergocalciferol") AND ("inflammation" OR "interleukin-6" OR "c-reactive protein").

To be included in this review, studies were limited to RCTs (including both parallel and cross-over study designs) to ensure the effects of interventions on outcomes were compared to placebo or control group receiving no treatment. Studies were required to meet the following inclusion criteria: (1) conducted in humans aged 45 years or older; (2) included at least one specific nutritional or pharmacological intervention arm; (3) assessed the effect of treatment on an outcome of interest (IL-6 or CRP); (4) conducted in adults with baseline levels of IL-6 between 2.5 and 30 pg/ml and/or baseline levels of CRP between 2 and 10 mg/L, according to the most well accepted cut-off levels indicating chronic LGI (Ferrucci et al., 1999; Ockene et al., 2001; Ridker et al., 2008; Ridker et al., 2001; Sabatine et al., 2007; Steinmetz et al., 1995); (5) carried out for four weeks or longer; (6) with a sample size of at least 15 per group; and (7) written in the English language. In addition, studies with the following characteristics were excluded: (1) involving patients with infections, acute inflammatory diseases, acute coronary syndrome, chronic kidney disease, chronic liver and lung diseases, inflammatory bowel diseases, autoimmune disorders, cancers, or participants undergoing surgical procedures; (2) with another intervention co-occurring; and (3) with intravenous administration of treatment.

Articles were initially screened based on title and abstract by three study authors (C.C., R.T.M. and S.A.L.), with the full text sought if the abstract did not provide sufficient information to draw a conclusion

Table 1
Selection criteria of compounds to include in the systematic review.

Compounds	Safety	Tolerability, acceptability	Innovation	Affordability	Evidence from RCTs
ACEIs	+	–	+	+	+
ARBs	+	+	+	+	+
Beta-blockers	+	–	+	+	+
Spironolactone	+	+	+	+	–
Metformin	+	+	+	+	+
ω − 3	+	+	+	+	+
Probiotics	+	+	+	+	+
Resveratrol	+	+	+	+	+
Vitamin D	+	+	+	+	+
Calcitriol	–	–	+	+	–
Thiazolidinediones	–	–	+	+	+
Sulfonylureas	–	–	+	+	+
Statins, fibrates	–	–	+	+	+
Anti-TNF-α, −IL6,-IL1; methotrexate, leflunomide, thalidomide, rapamycin, cyclosporin A, tacrolimus	–	–	–	–	+
Corticosteroids, aspirin, paracetamol, NSAIDs, cox-2 inhibitors, sulfasalazine, mesalamine	–	–	–	+	+
N-acetylcysteine	+	+	+	–	–
Imatinib, gemcitabine	–	–	+	–	–
Fluoroquinolones, macrolides	–	–	+	+	–
Ribavirin, ritonavir	–	–	+	–	–
Estrogen, Raloxifene	–	–	+	+	+
Melatonin	+	+	+	+	–
Ursodeoxycholic acid	?	?	+	+	–
Vitamin B6, C, E; β-Carotene	+	+	+	+	–
Foods, herbs and spices (apple juice, black raspberry extract, blueberry, cocoa, curcumin, garlic, *Ginkgo biloba* extract, ginseng, pomegranate extract, strawberry extracts)	+	+	+	+	–
Other micronutrients (anthocyanins, astaxanthin, bromelain, capsaicin, epigallocatechin-3-gallate, genistein, glucosamine, glutamine, quercetin)	+	+	+	+	–

"+" positive evidence, "–" negative evidence, "?" evidence lacking. In bold the compounds that fulfilled all selection criteria. ARBs = angiotensin II receptor blockers, ACEIs = angiotensin-converting enzyme inhibitors, NSAIDs = non-steroidal anti-inflammatory drugs, Cox-2 = cyclooxygenase-2.

regarding eligibility for inclusion in the current review.

Reference lists of the articles were reviewed to identify additional relevant articles. Disagreement was resolved by discussion or in consultation with a senior author (S.D.A.). We contacted authors of primary studies to obtain any missing information.

2.2. Data extraction

The following details were extracted from each study: first author's name, publication year, sample size, details of study population (age, body mass index −BMI-, health status), study duration, study design, outcomes of interest measured at baseline, and at follow-up after the intervention. For example, the findings from studies testing different dosages of compounds or including different sub-studies, were extracted separately. In the article of Bahr et al. (2011) we excluded results referring to treatment with telmisartan 80 mg because mean age in that group was less than 45, therefore, we considered only findings from groups under telmisartan 160 mg and placebo. All values were converted to the same units of measure: pg/ml for IL-6 and mg/L for CRP.

2.3. Risk of bias assessment

All included studies were assessed for quality using the Cochrane Collaboration's tool (Higgins et al., 2011) from a study author (C.C.). Each study was assigned a rating (low, unclear or high risk of bias) related to six domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, and selective outcome reporting. The reliability of assessment was ensured by revision and consultation with a senior author (S.D.A.).

2.4. Statistical analysis

Each study's effect size, or standardized mean difference (SMD) was calculated by comparing mean and standard deviation of IL-6 or CRP at follow-up measurement, between treatment and control group (Borenstein, 2009). Hedges'g was used to adjust the effect size, and an overall weighted average effect size for each compound was calculated based on each study's sample size (Borenstein, 2009). In accordance with convention, effect sizes of compounds were classified as small (−0.2), moderate (−0.5) and large (−0.8) (Cohen, 1992). Z statistics were calculated by comparing effect size difference over pooled standard deviation between every two compounds. The z-test was used to perform pairwise comparisons of effects between compounds and to test if each compound was significantly different from the overall mean of all compounds (Borenstein, 2009). Fixed-effects model was used as we applied strict inclusion criteria and assumed the population and effect would be similar across studies (Borenstein, 2009). Heterogeneity of effects across studies was estimated by I^2 statistics. It measures percentage of variation that is caused by heterogeneity between studies, and is larger when heterogeneity increases (Borenstein, 2009). A meta-regression was conducted, for all the selected compounds, to estimate the influence of dosage and treatment duration on effect size. Funnel plots and Egger's tests were utilized to detect bias in meta analyses (Borenstein, 2009). All statistical analyses were performed in R 3.3.2 (R Core Team, 2013). Each P-value is based on two-sided alternative hypothesis, and a level of 0.05 or below was considered statistically significant.

3. Results

3.1. Search results and study selection

A total of 858 articles were identified and assessed for eligibility. Based on titles and abstracts, 569 papers were excluded. Following full

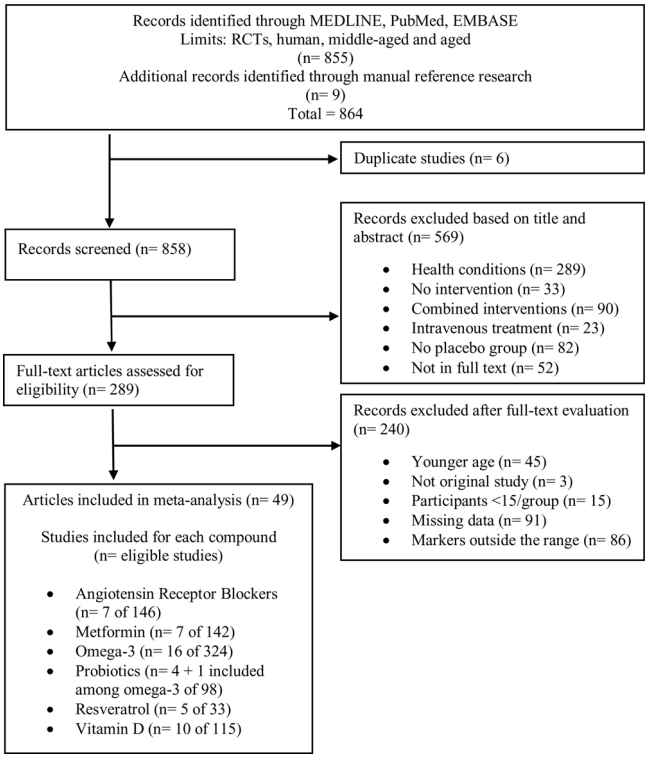

Fig. 1. Flow diagram of study selection process.

text revision of remaining 289 articles, other 240 studies were excluded. Overall, 49 RCTs (Bahr et al., 2011; Bays et al., 2013; Bitzur et al., 2010; Bo et al., 2016; Breslavsky et al., 2013; Caballero et al., 2004; Chandler et al., 2014; Darghosian et al., 2015; Dawczynski et al., 2013; De Jager et al., 2005; de Jager et al., 2014; Duggan et al., 2015; Ebrahimi et al., 2009; Feher et al., 2014; Gagnon et al., 2014; Goldberg et al., 2014; Hass et al., 2014; Hutchins et al., 2013; Krysiak et al., 2011, 2013; Link et al., 2006; Magyar et al., 2012; Mazloom et al., 2013; Militaru et al., 2013; Mohamadshahi et al., 2014; Murphy et al., 2007; Nodari et al., 2011; Ogino et al., 2010; Paoli et al., 2015; Persson et al., 2006; Pooya et al., 2010; Pot et al., 2009; Pradhan et al., 2009; Rajkumar et al., 2014; Sadiya et al., 2015; Schiano et al., 2008; Shaseb et al., 2016; Sinha-Hikim et al., 2015; Sokol et al., 2012; Stricker et al., 2012; Tome-Carneiro et al., 2012; Tousoulis et al., 2008; Troseid et al., 2009; Valentini et al., 2015; van der Zijl et al., 2011; Witte et al., 2014; Xu et al., 2015; Zhao et al., 2009; Zittermann et al., 2009) were selected for the final analysis (one RCT (Rajkumar et al., 2014) was eligible among both omega-3 and probiotics). Fig. 1 presents the flow diagram of the study selection process, and the stated reason specific articles were excluded followed the order of inclusion/exclusion criteria listed in the Methods section.

3.2. Quality assessment

Figs. 2 and Fig. A.1 (Supplementary materials) summarize the distribution of the risk of bias across all included studies. Incomplete outcome data, allocation concealment, random sequence generation, and blinding of participants and personnel were the major concerns as potential sources of bias. Thirty studies had unclear risk of bias, eight studies had high risk of bias in one category, and two had high risk of bias in two categories.

3.3. Study findings for specific compounds

3.3.1. ARBs

Seven of 146 potential articles involving 528 participants met our inclusion criteria (Bahr et al., 2011; Hass et al., 2014; Link et al., 2006; Ogino et al., 2010; Persson et al., 2006; Tousoulis et al., 2008; van der Zijl et al., 2011). The included studies tested five different ARBs: losartan, valsartan, candesartan, irbesartan and telmisartan. The majority of the trials were double-blind and placebo-controlled. Only two studies did not have a placebo group, but the control group was represented by people who received usual antihypertensive treatment (other than RAS inhibitors) or no antihypertensive treatment (Hass et al., 2014; Tousoulis et al., 2008). Table 2 presents key characteristics of the included studies.

In the intervention groups, mean levels of IL-6 and CRP at baseline were 2.8 ± 1.4 pg/ml and 4.4 ± 3.3 mg/L, respectively. Overall, after treatment, IL-6 levels (SMD: −0.37, 95% confidence interval (CI): −0.59 to −0.16, $p < 0.001$; Fig. 3) and CRP levels (SMD: −0.2, 95% CI: −0.39 to −0.02, $p < 0.05$; Fig. 4) significantly decreased compared to placebo/control groups. There was not significant dosage or treatment duration effects for either IL-6 or CRP. We found a high heterogeneity across the studies ($I^2 = 93.8\%$ for IL-6 studies, $I^2 = 85.1\%$ for CRP studies), but no significant risk of small-study effect (Fig. A.2, Supplementary materials).

3.3.2. Metformin

Seven of 142 potential studies described the effects of metformin in 3247 participants with mean CRP levels of 3.8 mg/L (Caballero et al., 2004; De Jager et al., 2005; de Jager et al., 2014; Goldberg et al., 2014; Krysiak et al., 2013; Pradhan et al., 2009; Xu et al., 2015). No study with the above mentioned inclusion criteria reported IL-6 levels. Thus, all the included studies investigated the effect of metformin on CRP levels. Table 3 shows the characteristics of each trial.

Metformin treatment significantly reduced serum CRP concentrations compared to placebo (SMD: −0.16, 95% CI: −0.22 to −0.09, $p < 0.0001$, $I^2 = 79.9\%$; Fig. 4). Analysis adjusted for the dosages

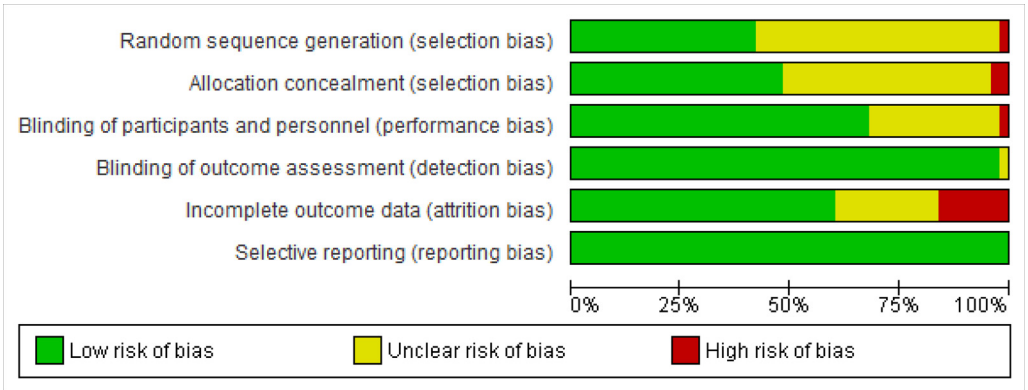

Fig. 2. Risk of bias assessment. Percentage of studies having high, unclear or low risk of bias.

Table 2
General characteristics of randomized controlled trials testing the effect of angiotensin receptor blockers (ARBs) supplementation on IL-6 and CRP.

Study	N	Age (years)ˆ	BMI (kg/m^2)ˆ	Population/ Health status	Duration	Intervention	Baseline levelsˆ	Δ levels from baselineˆ
IL-6 (pg/ml) studies								
Bahr et al. (2011)	telmisartan 160 mg: 19 PLA: 18	telmisartan 160 mg: 50 ± 10.4 PLA: 45.1 ± 11.9	telmisartan 160 mg: 34.6 ± 6.5 PLA: 32.7 ± 7.1	Patients with metabolic syndrome	14 weeks	telmisartan 160 mg/d, or placebo.	telmisartan 160 mg: 2.5 ± 1.9 PLA: 2.1 ± 1.7	telmisartan 160 mg: +0.2 PLA: +0.1
Ogino et al. (2010)	16	63 ± 4	25.8 ± 1.4	Patient with CHF	16 weeks	cross-over study design with losartan 100 mg/d (3 patients 50 mg/d) vs placebo	4.0 ± 0.5	losartan: −1.3* PLA: −0.2
Persson et al. (2006)	irbesartan: 143 PLA: 126	irbesartan: 57.3 ± 8.0 PLA: 58.4 ± 9.0	irbesartan: 29.8 ± 4.4 PLA: 30.4 ± 4.3	Patients with T2DM and microalbuminuria	96 weeks	irbesartan 300 mg/d vs placebo	[b]irbesartan: 2.98 (2.65–3.36) PLA: 3.12 (2.80–3.48)	irbesartan: +0.15**(vs PLA) PLA: +0.37
Link et al. (2006)	telmisartan: 21 PLA: 21	telmisartan: 56.4 ± 7.1 PLA: 58.5 ± 11.6	telmisartan: 27.3 ± 3.6 PLA: 26.9 ± 2.9	Patients with stable CAD and essential hypertension	12 weeks	telmisartan 40 mg/d vs placebo	telmisartan: 2.5 ± 0.6 PLA: 3.8 ± 1.4	telmisartan: −1.1 PLA: −1.2
CRP (mg/L) studies								
Hass et al. (2014)	candesartan 32 mg: 22 candesartan 16 mg: 23 CNT: 22	candesartan 32 mg: 63.1 ± 6.2 candesartan 16 mg: 61.6 ± 8.2 CNT: 62.7 ± 8.0	candesartan 32 mg: 32.4 ± 3.4 candesartan 16 mg: 30.6 ± 4.2 CNT: 31.5 ± 4.6	Patients with hypertension	24 weeks	candesartan 32 mg or candesartan 16 mg or patients that received antihypertensive treatment other than ARBs or ACEIs	candesartan 32 mg: 7 ± 5 candesartan 16 mg: 4 ± 4 CNT: 3 ± 5	candesartan 32 mg: +2 candesartan 16 mg: +1 CNT: +5
van der Zijl et al. (2011)	valsartan: 21 PLA: 20	56.7 ± 1	valsartan: 29.0 ± 0.7 PLA: 28.2 ± 1.0	Individuals with impaired glucose metabolism	26 weeks	valsartan 320 mg/d or placebo	valsartan: 2.8 ± 1.1 PLA: 2.8 ± 0.6	valsartan: −0.64 PLA: +0.18
Tousoulis et al. (2008)	irbesartan: 20 CNT: 20	irbesartan: 58.4 ± 1.9 CNT: 60.0 ± 2.9	irbesartan: 24.5 ± 0.27 CNT: 24.1 ± 0.28	Normotensive patients with CAD	4 weeks	irbesartan 75 mg/d or no antihypertensive agent	irbesartan: 4.08 ± 0.58 CNT: 3.5 ± 0.79	irbesartan: −1.43* CNT: −1.2
Persson et al. (2006)	irbesartan: 143 PLA: 126	irbesartan: 57.3 ± 8.0 PLA: 58.4 ± 9.0	irbesartan: 29.8 ± 4.4 PLA: 30.4 ± 4.3	Patients with T2DM and microalbuminuria	96 weeks	irbesartan 300 mg/d vs placebo	[b]irbesartan: 3.13 (2.62–3.74) PLA: 2.96 (2.43–3.61)	irbesartan: -0.29*** (vs PLA) PLA: +0.49
Link et al. (2006)	telmisartan: 21 PLA: 21	telmisartan: 56.4 ± 7.1 PLA: 58.5 ± 11.6	telmisartan: 27.3 ± 3.6 PLA: 26.9 ± 2.9	Patients with stable CAD and essential hypertension	12 weeks	telmisartan 40 mg/d vs placebo	telmisartan: 3.1 ± 0.5 PLA: 3.0 ± 0.5	telmisartan: −0.1 PLA: +2.1

IL = interleukin, CRP = C-reactive protein, N = number of participants, Δ = change, INT = intervention, PLA = placebo, CNT = control, CHF = chronic heart failure, T2DM = type 2 diabetes mellitus, CAD = coronary artery disease, ACEIs = angiotensin-converting enzyme inhibitors. ˆ = All values are means (± standard deviation (SD)). b = mean (95% confidence interval (CI)). Change data are defined as the follow-up minus the baseline value. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

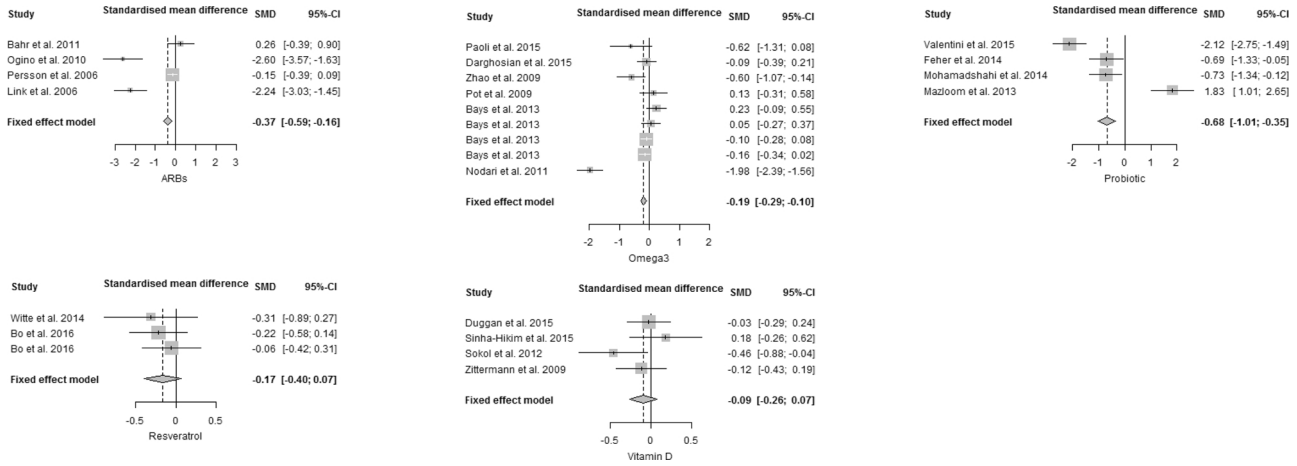

Fig. 3. Forest plots for effect of interventions compared to placebo group on IL-6 levels. A standardized difference in means < 0 favours intervention and > 0 favours the placebo arm. Box size represents study weighing. Diamond represents overall effect size and 95% confidence intervals.

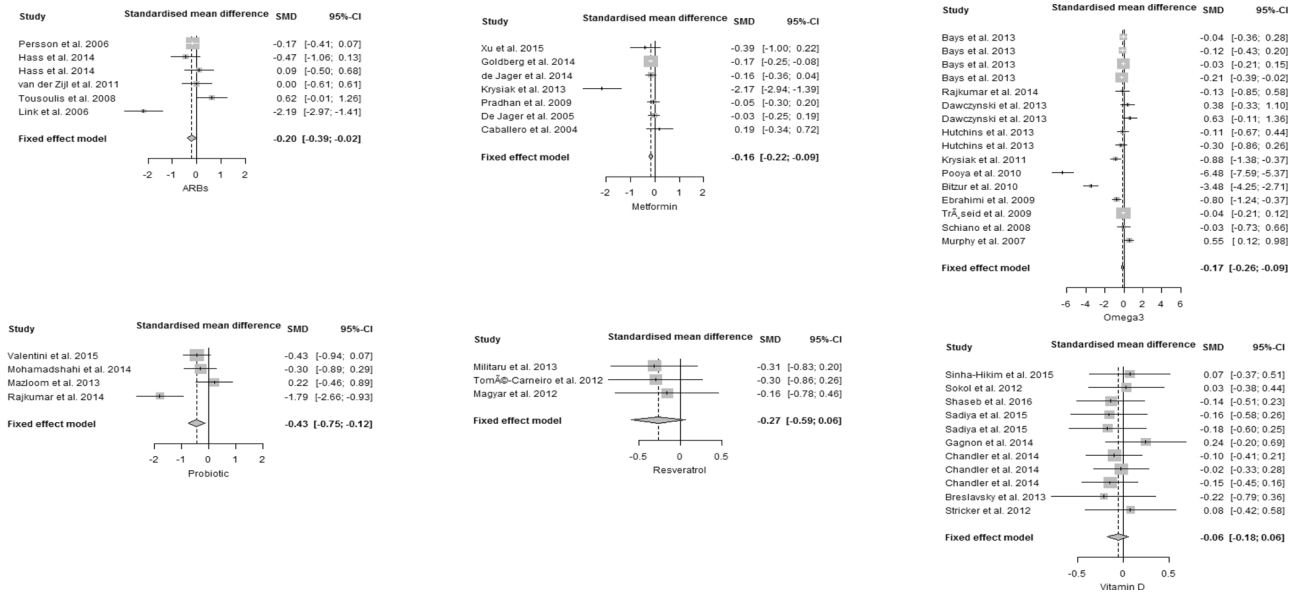

Fig. 4. Forest plots for effect of interventions compared to placebo group on CRP levels. A standardized difference in means < 0 favours intervention and > 0 favours the placebo arm. Box size represents study weighing. Diamond represents overall effect size and 95% confidence intervals.

showed that a greater reduction of CRP levels was associated with higher doses of metformin (-0.87, standard error (SE): 0.39; $p < 0.05$), but there were not significant treatment duration effects. Although visual inspection of the Funnel plot showed asymmetry (Fig. A.3, Supplementary materials) confirmed by Egger's test ($p = .05$), excluding data from Krysiak et al. (2013), the effect size of metformin treatment did not change significantly.

3.3.3. Omega-3

Sixteen of 324 potential studies described the effects of omega-3 in 2576 participants (Bays et al., 2013; Bitzur et al., 2010; Darghosian et al., 2015; Dawczynski et al., 2013; Ebrahimi et al., 2009; Hutchins et al., 2013; Krysiak et al., 2011; Murphy et al., 2007; Nodari et al., 2011; Paoli et al., 2015; Pooya et al., 2010; Pot et al., 2009; Rajkumar et al., 2014; Schiano et al., 2008; Troseid et al., 2009; Zhao et al., 2009). Characteristics of included studies are displayed in Table 4.

On average, at baseline in omega-3 groups, IL-6 levels were 10.6 ± 6.3 pg/ml and CRP levels were 3.5 ± 2.0 mg/L. IL-6 levels were significantly lower after omega-3 supplementation compared to the respective controls (SMD: −0.19, 95% CI: −0.29 to −0.10, $p < 0.0001$; Fig. 3). Omega 3 interventions resulted in a significantly more pronounced decrease in CRP levels as compared to placebo (SMD: −0.17, 95% CI: −0.26 to −0.09, $p < 0.0001$; Fig. 4). Meta-regression identified a significant decrease of IL-6 levels as the duration of the treatment increased (−0.04, SE: 0.01, $p < 0.0001$), but no significant treatment duration effects for CRP. There were also not significant dosage effects for either IL-6 or CRP. Heterogeneity was high for both IL-6 ($I^2 = 90.9\%$) and CRP studies ($I^2 = 93.6\%$). There was no evidence of small-study effect (Egger's test: $p = .32$) for IL-6. Since there was evidence of small-study effect for CRP (Egger's test: $p < 0.001$, Fig. A.4, Supplementary materials), we performed a sensitivity analysis excluding data from Pooya et al. (2010) and Bitzur et al. (2010). After

Table 3
General characteristics of randomized controlled trials testing the effect of metformin supplementation on CRP.

Study	N	Age (years)^	BMI (kg/m^2)^	Population/ Health status	Duration	Intervention	Baseline levels^	Δ levels from baseline^
CRP (mg/L) studies								
Xu et al. (2015)	INT: 21 PLA: 21	INT: 55.2 ± 10.4 PLA: 55.1 ± 10.9	–	Patients with carotid artery atherosclerosis	12 weeks	metformin 1000 mg/d	[a]INT: 3.5 (1.3–9.9) PLA: 3.1 (0.9-7.8)	INT: −2.2** PLA: −0.2
Goldberg et al. (2014)	MET: 1073 PLA: 1082	MET: 50.9 ± 10.3 PLA: 50.3 ± 10.4	MET: 33.9 ± 6.6 PLA: 34.2 ± 6.7	Participants at high risk for T2DM	3.4 years	metformin 1700 mg/d or placebo or intensive lifestyle	[b]MET: 3.34 (3.13-3.57) PLA: 3.52 (3.30-3.75)	MET: −0.36* (vs PLA) PLA: −0.08
de Jager et al. (2014)	MET: 196 PLA: 194	MET: 64 ± 10 PLA: 59 ± 11	MET: 30 ± 5 PLA: 30 ± 5	Patients with T2DM treated with insulin	4.3 years	metformin 850 mg or placebo (one to three times daily) added to insulin therapy	[b]MET: 3.06 (2.63-3.56) PLA: 3.06 (2.61-3.58)	MET: −0.45* (vs PLA) PLA: +0.06
Krysiak et al. (2013)	FEN + MET: 22 FEN + PLA: 20	FEN + MET: 50 ± 4 FEN + PLA: 51 ± 4	FEN + MET: 28.5 ± 2.6 FEN + PLA: 28.3 ± 2.2	Patients with isolated IGT	12 weeks	fenofibrate 200 mg/d + metformin 3000 mg/d or fenofibrate 200 mg/d + placebo	FEN + MET: 2 ± 0.5 FEN + PLA: 2.2 ± 0.5	FEN + MET: −0.8** FEN + PLA: −0.1
Pradhan et al. (2009)	MET: 126 PLA: 124	MET: 53.8 ± 11.5 PLA: 54.0 ± 10.9	MET: 36.2 ± 8.1 PLA: 37.2 ± 8.2	Patients with T2DM	14 weeks	2 × 2 factorial trial of insulin glargine and placebo-controlled metformin (500 mg/d up-titrated to max 2000 mg/d)	[b]MET: 4.3 (3.6-5.1) PLA: 4.7 (3.9-5.6)	MET: −0.7 PLA: −0.9
De Jager et al. (2005)	INT: 150 PLA: 163	INT: 63 ± 9 PLA: 59 ± 11	INT: 29.9 ± 5.2 PLA: 29.5 ± 4.6	Patients with T2DM treated with insulin	16 weeks	metformin 850 mg or placebo (one to three times daily) added to insulin therapy	[b]INT: 3.26 (2.80–3.78) PLA: 3.27 (2.80–3.81)	INT: −0.02 PLA: +0.07
Caballero et al. (2004)	INT: 29 PLA: 26	INT: 47.7 ± 9.8 PLA: 49.3 ± 9.6	INT: 30.0 ± 6.2 PLA: 29.8 ± 3.5	Participants with IGT	16 weeks	metformin 2000 mg/d or placebo	INT: 5.5 ± 1.3 PLA: 5.3 ± 0.7	INT: −0.1 PLA: −0.1

IL = interleukin, CRP = C-reactive protein, N = number of participants, Δ = change, INT = intervention, CNT = control, PLA = placebo, T2DM = type 2 diabetes, MET = metformin, IGT = impaired glucose tolerance, FEN = fenofibrate. ^ = All values are means (± standard deviation (SD)). a = median (interquartile range). b = mean (95% confidence interval (CI)). Change data are defined as the follow-up minus the baseline value. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 4
General characteristics of randomized controlled trials testing the effect of omega-3 supplementation on IL-6 and CRP.

Study	N	Age (years)^	BMI (kg/m^2)^	Population/ Health status	Duration	Intervention	Baseline levels^	Δ levels from baseline^
IL-6 (pg/ml) studies								
Paoli et al. (2015)	MD + ω3: 16 MD: 18	MD + ω3: 58.1 ± 6.0 MD: 56.3 ± 5.1	MD + ω3: 29.2 ± 2.3 MD: 29.3 ± 2.4	Male overweight participants	4 weeks	ketogenic MD with and without supplementation of omega-3 230 mg/d	MD + ω3: 6.55 ± 1.41 MD: 6.13 ± 0.81	MD + ω3: −2.9* MD: −1.75
Darghosian et al. (2015)	INT: 126 PLA: 64	INT: 62 ± 12 PLA: 61 ± 11	INT: 30.1 ± 7.2 PLA: 31.9 ± 7.3	Patients with paroxysmal or persistent atrial fibrillation	24 weeks	4 g/d of omega-3 or placebo (corn oil)	[a]INT: 2.8 (1.5-4.4) PLA: 2.5 (1.3–4.5)	INT: −0.6 PLA: −0.1
Zhao et al. (2009)	INT: 38 PLA: 37	INT: 74 ± 6 PLA: 71 ± 10	INT: 24.7 ± 3.6 PLA: 24.0 ± 2.9	Patients with CHF	12 weeks	2 g/d of omega 3 or placebo	INT: 11.5 ± 7.9 PLA: 11.1 ± 10.2	INT: −3.6** PLA: +1.7
Pot et al. (2009)	INT: 39 PLA: 38	INT: 58 ± 4.3 PLA: 59.5 ± 5.3	INT: 26.5 ± 3.2 PLA: 26.6 ± 3.6	Healthy participants	12 weeks	1.5 g/d of omega-3 or placebo (high oleic sunflower oil)	[a]INT: 8.00 (1.66-31.3) PLA: 3.42 (2.64-50)	INT: −1.16 PLA: 0
Bays et al. (2013)	IPE 4 g/d: 77 IPE 2 g/d: 76 PLA: 76	IPE 4 g/d: 51.9 ± 10.2 IPE 2 g/d: 53.4 ± 9.3 PLA: 53.4 ± 8.3	IPE 4 g/d: 30.4 ± 4.3 IPE 2 g/d: 30.8 ± 4.2 PLA: 31.0 ± 4.2	Hypertriglyceridemic patients from MARINE study	12 weeks	IPE 4 g/d vs IPE 2 g/d vs placebo	[a]IPE 4 g/d: 2.3 (3.34) IPE 2 g/d: 3.0 (2.78) PLA: 2.5 (4.12)	IPE 4 g/d: +0.1 IPE 2 g/d: 0 PLA: −0.2
Bays et al. (2013)	IPE 4 g/d: 233 IPE 2 g/d: 236 PLA: 233	IPE 4 g/d: 61.6 ± 10 IPE 2 g/d: 61.8 ± 9.4 PLA: 61.2 ± 10.5	IPE 4 g/d: 32.7 ± 4.9 IPE 2 g/d 32.9 ± 4.9 PLA: 33.0 ± 5.0	Hypertriglyceridemic patients from ANCHOR study	12 weeks	IPE 4 g/d vs IPE 2 g/d vs placebo	[a]IPE 4 g/d: 2.7 (2.61) IPE 2 g/d: 2.4 (2.01) PLA: 3.2 (3.23)	IPE 4 g/d: −0.1 IPE 2 g/d: +0.3 PLA: −0.3
Nodari et al. (2011)	INT: 67 PLA: 66	INT: 61 ± 11 PLA: 64 ± 9	INT: 25.9 ± 2.3 PLA: 25.7 ± 2.22	Patients with CHF	48 weeks	2 g/d of omega 3 or placebo (olive oil)	INT: 11.0 ± 6.0 PLA: 10.1 ± 4.5	INT: −7.47*** PLA: +1.1***
CRP (mg/L) studies								
Rajkumar et al. (2014)	ω3: 15 PRO: 15 PRO + ω3: 15 PLA: 15	49	28.79	Overweight healthy adults	6 weeks	VSL#3 1 cps/d, omega-3: 180 mg EPA + 120 mg DHA/d, VSL#3 + omega-3 or placebo	ω3: 5.60 ± 0.74 PRO: 5.60 ± 0.52 PRO + ω3: 6.20 ± 0.41 PLA: 5.30 ± 0.58	ω3: −0.34* PRO: −1.24** PRO + ω3: −1.90** PLA: +0.05
Dawczynski et al. (2013)	HIGH: 16 LOW: 17 PLA: 14	HIGH: 61.8 ± 7.1 LOW: 61.6 ± 11.8 PLA: 58.2 ± 7.4	HIGH: 25.9 ± 3.6 LOW: 26.8 ± 3.9 PLA: 26.1 ± 3.8	Hypertriglyceridemic participants	10 weeks	yogurt supplemented with omega-3 0.8 g/d (LOW), 3 g/d (HIGH) or placebo (commercial fruit yogurt)	HIGH: 2.93 ± 2.76 LOW: 3.87 ± 4.19 PLA: 1.50 ± 1.64	HIGH: +1.11 LOW: −1.24 PLA: 0.25
Hutchins et al. (2013)	25	58.6 ± 6.3	30.4 ± 5.3	Overweight or obese individuals with pre-diabetes	12 weeks	crossover trial with 0, 2.9 g/d (LOW), or 5.8 g/d (HIGH) of ALA	HIGH: 3.2 ± 2.8 LOW: 3.0 ± 3.2 CNT: 2.9 ± 3.0	HIGH: −0.4 ± 1.2 LOW: +0.4 ± 2.4 CNT: +0.9 ± 2.1
Bays et al. (2013)	IPE 4 g/d: 77 IPE 2 g/d: 76 PLA: 76	IPE 4 g/d: 51.9 ± 10.2 IPE 2 g/d: 53.4 ± 9.3 PLA: 53.4 ± 8.3	IPE 4 g/d: 30.4 ± 4.3 IPE 2 g/d: 30.8 ± 4.2 PLA: 31.0 ± 4.2	Hypertriglyceridemic patients from MARINE study	12 weeks	IPE 4 g/d vs IPE 2 g/d vs placebo	[a]IPE 4 g/d: 2.2 (3.10) IPE 2 g/d: 2.0 (2.70) PLA: 1.8 (3.05)	IPE 4 g/d: 0** (vs PLA) IPE 2 g/d: +0.4 PLA: +0.7
Bays et al. (2013)	IPE 4 g/d: 233 IPE 2 g/d: 236 PLA: 233	IPE 4 g/d: 61.6 ± 10 IPE 2 g/d: 61.8 ± 9.4 PLA: 61.2 ± 10.5	IPE 4 g/d: 32.7 ± 4.9 IPE 2 g/d 32.9 ± 4.9 PLA: 33.0 ± 5.0	Hypertriglyceridemic patients from ANCHOR study	12 weeks	IPE 4 g/d vs IPE 2 g/d vs placebo	[a]IPE 4 g/d: 2.2 (2.70) IPE 2 g/d: 1.9 (2.90) PLA: 2.2 (4.00)	IPE 4 g/d: -0.2*** (vs PLA) IPE 2 g/d: +0.6 PLA: +0.4
Krysiak et al. (2011)	ω3: 34 PLA: 32	ω3: 53.1 ± 3.5 PLA: 52.5 ± 3.1	ω3: 28.6 ± 2.8 PLA: 28.3 ± 2.4	Hypertriglyceridemic participants	12 weeks	omega-3 2 g/d or placebo	ω3: 3.3 ± 0.5 PLA: 3.1 ± 0.3	ω3: −0.8 PLA: −0.2
Pooya et al. (2010)	INT: 40 PLA: 41	INT: 56.4 ± 9.2 PLA: 52.7 ± 10.6	INT: 27.7 ± 3.4 PLA: 26.1 ± 5.0	Patients with T2DM	8 weeks	2.7 g/d of omega-3 or placebo (sunflower oil)	INT: 2.70 ± 0.02 PLA: 3.15 ± 0.36	INT: −0.22 PLA: +0.65
Bitzur et al. (2010)	INT: 34 PLA: 33	INT: 51.0 ± 1.9 PLA: 48.3 ± 1.6	INT: 27.8 ± 0.8 PLA: 28.0 ± 0.6	Participants with mixed hyperlipidemia	12 weeks	1.6 g free plant sterols and 1.3 g EPA + DHA or 4 g corn oil (placebo) daily.	INT: 3.1 ± 0.6 PLA: 3.3 ± 0.4	INT: −0.6 ** (vs PLA) PLA: +1.2
Ebrahimi et al. (2009)	INT: 47 CNT: 42	INT: 53.5 ± 12.7 CNT: 52.3 ± 11.1	INT: 30.3 ± 5.2 CNT: 30.4 ± 6.1	Participants with metabolic syndrome	24 weeks	single capsule containing 180 mg EPA and 120 mg DHA daily, or no supplementation (control)	[a]INT: 9.37 (5.4–19.39) CNT: 7.73 (5.02-16.32)	INT: −6.25** CNT: −0.93
Troseid et al. (2009)	ω3: 282 PLA: 281	[a]70 (67–73)	[a]26.5 (24.1- 28.7)	Elderly men with high risk of cardiovascular disease	144 weeks	randomized 2 × 2 factorial-designed trial comparing Mediterranean like diet, omega-3 2.4 g/d, or combination.	[a]ω3: 3.58 (4.08) PLA: 3.13 (4.23)	ω3: −0.66* PLA: −0.09
Schiano et al. (2008)	INT: 16 CNT: 16	[a]INT: 66 (58–71) CNT: 66 (59–73)	[a]INT: 27 (25.8- 30) CNT: 26.8 (24.4- 29.7)	Patients with PAD	12 weeks	2 g/d of omega-3	[a]INT: 2.6 (2.1–5.8) CNT: 3.1 (2.1–3.9)	INT: +0.3 CNT: −0.1

(*continued on next page*)

Table 4 (*continued*)

Study	N	Age (years)^	BMI (kg/m^2)^	Population/ Health status	Duration	Intervention	Baseline levels^	Δ levels from baseline^
Murphy et al. (2007)	INT: 42 CNT: 44	INT: 50.4 ± 14.5 CNT: 50.2 ± 9.4	INT: 31.4 ± 5.0 CNT: 32.4 ± 5.1	Overweight volunteers with high levels of triacylglycerols	24 weeks	omega-3-enriched foods to achieve an EPA + DHA intake of 1 g/d or control foods (not enriched)	INT: 5.2 ± 0.7 CNT: 3.9 ± 0.4	INT: +0.4 CNT: +1.2

IL = interleukin, CRP = C-reactive protein, N = number of participants, Δ = change, INT = intervention, CNT = control, PLA = placebo, CHF = chronic heart failure, PAD = peripheral artery disease, T2DM = type 2 diabetes, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid, MD = Mediterranean diet, PRO = probiotics, ω3 = omega-3, IPE = icosapent ethyl. ^ = All values are means (± standard deviation (SD)). a = median (interquartile range). Change data are defined as the follow-up minus the baseline value. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

removal of these two studies, the CRP-lowering effect of omega-3 was still significant.

3.3.4. Probiotics

Five of 98 potential studies investigated the effect of probiotics in a total of 210 participants (Feher et al., 2014; Mazloom et al., 2013; Mohamadshahi et al., 2014; Rajkumar et al., 2014; Valentini et al., 2015). Table 5 shows the characteristics of included studies.

On average, concentration of IL-6 and CRP at baseline in intervention groups were 13.8 ± 2.0 pg/ml and 3.1 ± 1.0 mg/L, respectively. Probiotic supplementation significantly reduced both inflammatory biomarkers. The pooled effect sizes were −0.68 (95% CI: −1.01 to −0.35, $p < 0.0001$; Fig. 3) for IL-6 and −0.43 (95% CI: −0.75 to −0.12, $p < 0.01$; Fig. 4) for CRP. Moreover, meta-regression analysis showed a significant reduction of IL-6 levels as the duration of probiotic treatment increased (−1.13, SE: 0.39, $p < 0.01$), but there were not significant dosage effects for IL-6. There were not a sufficient number of studies to evaluate the dosage or treatment duration effects of probiotics on CRP. Heterogeneity was high for IL-6 studies ($I^2 = 94.7\%$) as well as CRP studies ($I^2 = 77.3\%$), with evidence of asymmetry at Funnel plot for IL-6 studies (Fig. A.5, Supplementary materials).

3.3.5. Resveratrol

Five of 33 potential studies were identified upon resveratrol effect in a total of 372 participants (Bo et al., 2016; Magyar et al., 2012; Militaru et al., 2013; Tome-Carneiro et al., 2012; Witte et al., 2014). Table 6 presents main characteristics of the studies.

Baseline serum concentrations of IL-6 and CRP in participants undergoing intervention were respectively 2.7 ± 2.1 pg/ml and 4.4 ± 2.8 mg/L. No significant effect was shown after resveratrol supplementation, with mean IL-6 decrease of −0.17 (95% CI: −0.40 to 0.07, $p > 0.05$; Fig. 3) and mean CRP decrease of −0.27 (95% CI: −0.59 to 0.06, $p > 0.05$; Fig. 4). There were not a sufficient number of studies to evaluate the dosage or treatment duration effects of resveratrol on either IL-6 or CRP. Heterogeneity was low for both IL-6 and CRP studies ($I^2 = 0\%$) and there was no evidence of small-study effect (Fig. A.6, Supplementary materials).

3.3.6. Vitamin D

Ten of 115 potential studies investigated the relationship between vitamin D supplementation (cholecalciferol or ergocalciferol) and levels of inflammatory biomarkers in 1314 adults (Breslavsky et al., 2013; Chandler et al., 2014; Duggan et al., 2015; Gagnon et al., 2014; Sadiya et al., 2015; Shaseb et al., 2016; Sinha-Hikim et al., 2015; Sokol et al., 2012; Stricker et al., 2012; Zittermann et al., 2009). Table 7 shows main characteristics of included trials.

At baseline in intervention groups, mean IL-6 and CRP levels were respectively 5.6 ± 9.4 pg/ml and 5.8 ± 6.6 mg/L. Vitamin D supplementation did not produce any significant reduction in either inflammatory biomarker compared to placebo. The pooled effect sizes were −0.09 (95% CI: −0.26 to 0.07, $p > 0.05$; Fig. 3) for IL-6 and −0.06 (95% CI: −0.18 to 0.06; $p > 0.05$, Fig. 4) for CRP. There was not significant dosage or treatment duration effects for either IL-6 or CRP. Heterogeneity was low for both IL-6 ($I^2 = 36.4\%$) and CRP studies ($I^2 = 0\%$) and there was no evidence of small-study effect (Fig. A.7, Supplementary materials).

3.4. Pooled analysis

Compared to the average effect size of all compounds, probiotics significantly reduced IL-6 levels (−0.68 vs −0.3, $z = -2.72$ $p < 0.01$). Conversely, vitamin D had a smaller effect than the mean change for all compounds (-0.09 vs −0.3, $z = 2.54$, $p < 0.05$). The effect of probiotics on IL-6 levels was also significantly larger compared to those of vitamin D (−0.68 vs −0.09, $z = -3.13$, $p < 0.01$), resveratrol (−0.68 vs −0.17, $z = -2.47$, $p < 0.05$) and omega-3

Table 5
General characteristics of randomized controlled trials testing the effect of probiotics supplementation on IL-6 and CRP.

Study	N	Age (years)^	BMI (kg/m^2)^	Population/ Health status	Duration	Intervention	Baseline levels^	Δ levels from baseline^
IL-6 (pg/ml) studies								
Valentini et al. (2015)	DIET: 31 DIET + VSL#3: 31	70.1 ± 3.9	26.8 ± 3.6	Healthy persons aged 65–85 years	8 weeks	web-based dietary advice (RISTOMED platform) alone or with supplementation of VSL#3 (2 cps/d) 112.5 × 10^9 CFU/capsule	DIET: 29.9 ± 9.1 DIET + VSL#3: 12.3 ± 1.8	DIET: +4.8 DIET + VSL#3: +5.4
Feher et al. (2014)	INT: 20 CNT: 20	INT: 45.15 ± 4.73 CNT: 45.95 ± 6.65	–	Patients with irritable eye syndrome	8 weeks	three softgels/d each containing lysate of *L. acidophilus* (1.25 × 10^9 CFU) and *B. longum* (1.35 × 10^9 CFU) vs control group (cod liver oil)	INT: 17.42 ± 10.52 CNT: 17.21 ± 5.26	INT: −4.55*** CNT: +0.1
Mohamadshahi et al. (2014)	INT: 22 CNT: 22	INT: 53 ± 5.9 CNT: 49 ± 7.08	INT: 28.36 ± 4.14 CNT: 29.22 ± 3.2	Patients with T2DM	8 weeks	300 g/d probiotic and conventional yogurts with *L. delbrueckii* subsp. *bulgaricus* and *S. thermophilus*. The probiotic yogurt also enriched with *B. animalis* subsp. *lactis* Bb12 and *L. acidophilus* strain La5 (3.7 × 10^6 CFU/g of both)	INT: 22.6 ± 2.81 CNT: 23.64 ± 3.31	INT: −0.42 CNT: +0.55
Mazloom et al. (2013)	INT: 16 PLA: 18	INT: 55.4 ± 8 PLA: 51.8 ± 10.2	INT: 27.97 ± 3.81 PLA: 27.24 ± 2.73	Patients with T2DM	6 weeks	probiotic capsules (*L. acidophilus, L. bulgaricus, L. bifidum, and L. casei*) 1500 mg/bid vs placebo (1000 mg magnesium stearate/bid)	INT: 4.51 ± 0.45 PLA: 4.38 ± 0.80	INT: −0.68 PLA: −1.29*
CRP (mg/L) studies								
Valentini et al. (2015)	DIET: 31 DIET + VSL#3: 31	70.1 ± 3.9	26.8 ± 3.6	Healthy persons aged 65–85 years	8 weeks	web-based dietary advice (RISTOMED platform) alone or with supplementation of VSL#3 (2 cps/d)	DIET: 3.6 ± 0.6 DIET + VSL#3: 2.9 ± 0.7	DIET: +0.2 DIET + VSL#3: −0.5
Rajkumar et al. (2014)	PRO: 15 ω3: 15 PRO + ω3: 15 PLA: 15	49	28.79	Overweight healthy adults	6 weeks	VSL#3 1 cps/d (112.5 × 10^9 CFU/capsule), omega-3: 180 mg EPA + 120 mg DHA/d, VSL#3 + omega-3 or placebo	PRO: 5.60 ± 0.52 ω3: 5.60 ± 0.74 PRO + ω3: 6.20 ± 0.41 PLA: 5.30 ± 0.58	PRO: −1.24** ω3: −0.34* PRO + ω3: −1.90** PLA: +0.05
Mohamadshahi et al. (2014)	INT: 22 CNT: 22	INT: 53 ± 5.9 CNT: 49 ± 7.08	INT: 28.36 ± 4.14 CNT: 29.22 ± 3.2	Patients with T2DM	8 weeks	300 g/d probiotic and conventional yogurts with *L. delbrueckii* subsp. *bulgaricus* and *S. thermophilus*. The probiotic yogurt also enriched with *B. animalis* subsp. *lactis* Bb12 and *L. acidophilus* strain La5 (3.7 × 10^6 CFU/g of both)	INT: 3.26 ± 1.36 CNT: 3.08 ± 1.54	INT: −0.46 CNT: +0.21
Mazloom et al. (2013)	INT: 16 PLA: 18	INT: 55.4 ± 8 PLA: 51.8 ± 10.2	INT: 27.97 ± 3.81 PLA: 27.24 ± 2.73	Patients with T2DM	6 weeks	probiotic capsules (*L. acidophilus, L. bulgaricus, L. bifidum, and L. casei*) 1500 mg/bid vs placebo (1000 mg magnesium stearate/bid)	INT: 3.17 ± 0.7 PLA: 2.17 ± 0.41	INT: +1.16 PLA: +1.89

IL = interleukin, CRP = C-reactive protein, N = number of participants, Δ = change, INT = intervention, CNT = control, PLA = placebo, PRO = probiotics, ω3 = omega-3, T2DM = type 2 diabetes. ^All values are means (± standard deviation (SD)). Change data are defined as the follow-up minus the baseline value. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 6
General characteristics of randomized controlled trials testing the effect of resveratrol supplementation on IL-6 and CRP.

Study	N	Age (years)^	BMI (kg/m^2)^	Population/ Health status	Duration	Intervention	Baseline levels^	Δ levels from baseline^
IL-6 (pg/ml) studies								
Bo et al. (2016)	HIGH: 62	HIGH: 65.0 ± 7.6	HIGH: 28.8 ± 3.9	Patients with T2DM	24 weeks	resveratrol 500 mg/day (HIGH), resveratrol 40 mg/day (LOW) or placebo	HIGH: 2.55 (2.15)	HIGH: −0.09
	LOW: 59	LOW: 64.9 ± 8.6	LOW: 29.5 ± 3.8				LOW: 2.71 (2.37)	LOW: +0.04
	PLA: 58	PLA: 65.4 ± 8.8	PLA: 28.2 ± 3.9				PLA: 2.83 (1.91)	PLA: +0.22
Witte et al. (2014)	INT: 23	INT: 64.8 ± 6.8	INT: 27.4 ± 1.9	Healthy older adults	26 weeks	200 mg of resveratrol and 320 mg of quercetin or placebo	INT: 2.9 ± 1.2	INT: −0.9**
	PLA: 23	PLA: 63.7 ± 5.3	PLA: 27.7 ± 1.6				PLA: 7.9 ± 19.8	PLA: −3.9*
CRP (mg/L) studies								
Militaru et al. (2013)	INT: 29	INT: 64.9 ± 5.8	°24–27	Participants with stable angina pectoris	8 weeks	resveratrol 20 mg/d	INT: 6.9 ± 2.5	INT: −1.7*
	CNT: 29	CNT: 64.2 ± 7.1					CNT: 6.6 ± 2.4	CNT: −0.7*
Tome-Carneiro et al. (2012)	GE-RES: 25	GE-RES: 62 ± 9	GE-RES: 32 ± 9	Participants at high risk of CVD	48 weeks	GE-RES: grape extract + 8.1 ± 0.5 mg of resveratrol per capsule. One cps/d for the first 6 months and 2 cps/d for the following 6 months, GE: conventional grape extract lacking resveratrol or placebo	GE-RES: 5 ± 3.7	GE-RES: −1.3*
	GE: 25	GE: 56 ± 11	GE: 31 ± 5				GE: 3.2 ± 2.5	GE: +0.1
	PLA: 24	PLA: 63 ± 9	PLA: 29 ± 3				PLA: 4.4 ± 4.3	PLA: +0.4
Magyar et al. (2012)	INT: 20	INT: 65.3 ± 9.7	INT: 29.3 ± 2.1	Participants with stable CAD	12 weeks	resveratrol 10 mg/day	INT: 3.64 ± 0.57	INT: +2.87
	PLA: 20	PLA: 67.4 ± 7.7	PLA: 28.1 ± 3.2				PLA: 3.27 ± 0.35	PLA: +3.76

IL = interleukin, CRP = C-reactive protein, N = number of participants, Δ = change, INT = intervention, CNT = control, PLA = placebo, T2DM = type 2 diabetes, RES = resveratrol, GE = grape extract, CVD = cardiovascular disease, CAD = coronary artery disease. ^All values are means (± standard deviation (SD)). Change data are defined as the follow-up minus the baseline value. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

(−0.68 vs −0.19, z = −2.80, p < 0.01), Table 8, Fig. 5. Furthermore, ARBs effect was significantly larger compared to that of vitamin D (−0.37 vs −0.09, z = −2.02, p < 0.05; Table 8, Fig. 5).

Average change of CRP levels considering all the included compounds was −0.21. None of the analyzed interventions yielded a significant difference in change of CRP concentrations compared to the mean effect of all compounds. However, in pairwise comparison, probiotics showed a significantly larger effect compared to vitamin D (−0.43 vs −0.06, z = −2.15, p < 0.05; Table 9, Fig. 6).

4. Discussion

The results of our meta-analysis suggest that many but not all compounds selected across a broad range of potential anti-inflammatory molecules have a significant effect on levels of IL-6 and CRP in middle-age and older adults with chronic LGI. Compared to placebo, ARBs, omega-3 and probiotics significantly reduced IL-6 levels, and ARBs, metformin, omega-3 and probiotics significantly reduced CRP levels. Effects ranged in size from small to large according to established definitions (Cohen, 1992). Two compounds, resveratrol and vitamin D, however, did not show any significant effect on the investigated inflammatory biomarkers.

In this review, among RAS inhibitors, we prioritized ARBs, also known as sartans, because of greater tolerability compared to angiotensin-converting enzyme inhibitors (ACEIs)(Caldeira et al., 2012). ARBs are widely used for the treatment of hypertension and cardiovascular diseases. They exhibit excellent safety profiles with minimal effects in normotensive patients. Our findings show that consumption of ARBs may provide a small to moderate reduction of IL-6 and CRP. Takagi et al. (2013) in a previous meta-analysis showed that telmisartan therapy is effective in reducing IL-6 (-0.38 pg/ml) and tumor necrosis factor (TNF)-α levels. The biological basis of ARBs effect on chronic LGI involves the blockade of angiotensin II type 1 receptor leading to inhibition of NF-κB signaling (Kleiber et al., 2010). In animal experiments, sartans have been shown to reduce IL-6 levels (Lin et al., 2014), improve memory (Ongali et al., 2014) and motor performance (Villapol et al., 2012) and protect against muscle loss (Burks et al., 2011). Moreover, a recent meta-analysis of RCTs and observational studies reported that the use of ARBs can reduce incidence risks by 35% for cognitive impairment and by 20% for AD (Zhuang et al., 2016). To date, no conclusion can be drawn on potential differences within drug class, due to dearth of available studies for each included sartan. Overall, these results suggest that people already treated with ARBs could take advantage from the anti-inflammatory effect of this therapy.

Metformin is the most commonly prescribed oral hypoglycemic drug and first line therapy in type 2 diabetes mellitus (T2DM). It has been used for over 60 years with an excellent safety record. A consistent body of data shows that metformin can increase health span and longevity through anti-inflammatory and anti-apoptotic pathways independent of its hypoglycemic effect (Barzilai et al., 2016; Saisho, 2015). Our results are consistent with these data, supporting a small but significant reduction of CRP levels following metformin administration. Evidence from the Diabetes Prevention Program study suggests the CRP lowering effect could be driven by weight loss achieved during metformin treatment (Haffner et al., 2005). The findings of our meta-analysis indicate this effect is significantly dependent upon metformin dosage; increased doses are associated with a greater reduction of CRP. This is in line with some findings from experimental models in which metformin reduced levels of several inflammatory mediators (IL-6, IL-1β, TNF-α, prostaglandin E_2, nitric oxide) in a dose-dependent manner (Hyun et al., 2013). Also for metformin, one of the biological mechanisms underpinning this anti-inflammatory effect was the inhibition of transcription factor NF-κB (Hyun et al., 2013; Li et al., 2009). Taken together these findings indicate metformin as a potential alternative strategy to caloric restriction in reducing inflammaging.

A large body of evidence indicates that omega-3, targeting NF-κB

Table 7
General characteristics of randomized controlled trials testing the effect of vitamin D supplementation on IL-6 and CRP.

Study	N	Age (years)^	BMI (kg/m^2)^	Population/ Health status	Duration	Intervention	Baseline levels^	Δ levels from baseline^
IL-6 (pg/ml) studies								
Duggan et al. (2015)	INT: 109 PLA: 109	INT: 60.3 ± 5.3 PLA: 59.0 ± 4.7	INT: 32.3 ± 5.5 PLA: 32.5 ± 6.1	Postmenopausal, overweight or obese women with vitamin-D insufficiency	48 weeks	vitamin D_3 2000 IU/d + a lifestyle-based weight-loss program or placebo + a lifestyle-based weight-loss program	[b]INT: 3.89 (3.33–4.53) PLA: 3.89 (3.15–4.79)	[b]INT: −0.48 PLA: −0.37
Sinha-Hikim et al. (2015)	INT: 40 PLA: 40	INT: 51.6 ± 7.7 PLA: 52.4 ± 6.7	INT: 32.5 ± 4.4 PLA: 32.9 ± 4.5	Participants with pre-diabetes and hypovitaminosis D	48 weeks	vitamin D_3 supplementation average dose (± SD) 85300 IU ± 16000/week i.m.	INT: 3.4 ± 2 PLA: 3.2 ± 2	INT: +0.3 PLA: +0.1
Sokol et al. (2012)	INT: 45 PLA: 45	INT: 55 ± 9.6 PLA: 56.9 ± 11.6	INT: 29.6 ± 6.2 PLA: 30.9 ± 7.6	Participants with CAD and vitamin D deficiency	12 weeks	ergocalciferol 50000 IU/week	[a]INT: 4.1 (6.8) PLA: 4.8 (4.5)	[a]INT: +0.59 PLA: +0.76
Zittermann et al. (2009)	INT: 82 PLA: 83	INT: 47.4 ± 10.3 PLA: 48.8 ± 10.1	INT: 33.7 ± 4.1 PLA: 33.0 ± 4.3	Healthy overweight participants and hypovitaminosis D	48 weeks	vitamin D_3 3332 IU/d or placebo while participating in a weight-reduction program	INT: 8.9 ± 15.2 PLA: 7.8 ± 12.3	INT: −3.5 ± 14.0 PLA: −1.9 ± 10.9
CRP (mg/L) studies								
Shaseb et al. (2016)	INT: 55 PLA: 57	INT: 54 ± 6.13 PLA: 55.9 ± 5.24	INT: 27.5 ± 2.8 PLA: 26.9 ± 2.8	Patient with T2DM and CAD	8 weeks	single-dose administration of either vitamin D 300000 IU i.m. or placebo	INT: 3.4 ± 3.2 PLA: 3.0 ± 2.3	INT: 0 PLA: +0.8
Sadiya et al. (2015)	INT: 45 PLA: 42	INT: 49 ± 8 PLA: 48 ± 8	INT:37.9 ± 6.1 PLA: 37.6 ± 7.7	Vitamin D-deficient obese, T2DM participants	24 weeks	two phases of 3 months each. In phase 1: vitamin D_3 6000 IU/d vs placebo capsules. In phase 2: vitamin D_3 3000 IU/d vs placebo	INT: 7.4 ± 7.6 PLA: 8.0 ± 9.2	12 weeks: INT: +0.4 PLA: +1.5 24 weeks: INT: +0.6 PLA: +2
Sinha-Hikim et al. (2015)	INT: 40 PLA: 40	INT: 51.6 ± 7.7 PLA: 52.4 ± 6.7	INT: 32.5 ± 4.4 PLA: 32.9 ± 4.5	Participants with pre-diabetes and hypovitaminosis D	48 weeks	vitamin D_3 supplementation average dose (± SD) 85300 IU ± 16000/week i.m.	INT: 5.6 ± 2.4 PLA: 5.6 ± 2.7	INT: +0.2 PLA: 0
Gagnon et al. (2014)	INT: 35 PLA: 45	INT: 53.8 ± 11.9 PLA: 55.3 ± 11.1	INT: 31.1 ± 5.7 PLA: 31.9 ± 6.2	Vitamin D-deficient participants at risk of T2DM	24 weeks	CA 1200 mg/d + vitamin D_3 2000–6000 IU/d to target 25(OH)D > 75 nmol/L	INT: 5.52 ± 10.82 PLA: 2.44 ± 2.15	INT: −1.9 PLA: +0.13
Chandler et al. (2014)	328	[a]51	[a]31	Healthy black population	12 weeks	vitamin D_3 1000 IU/d, 2000 IU/d or 4000 IU/d or placebo	[a]4000 IU: 2.23 (0.66-5.35) 2000 IU: 2.18 (0.6-6.74) 1000 IU: 1.95 (0.79-5.02) PLA: 2.74 (1.14-4.56)	[a]4000 IU: −0.25 2000 IU: +0.21 1000 IU: +0.26 PLA: −0.28
Breslavsky et al. (2013)	INT: 24 PLA: 23	INT: 66.8 ± 9.2 PLA: 65.8 ± 9.7	INT: 27.9 ± 5.2 PLA: 30.6 ± 5.1	Patients with T2DM	48 weeks	vitamin D_3 1000 IU/d	INT: 6 ± 5 PLA: 4 ± 3	INT: −2 PLA: +1
Stricker et al. (2012)	INT: 31 PLA: 31	INT: 72.9 ± 8.7 PLA: 74.8 ± 14.6	–	Patients with PAD	4 weeks	single oral supplementation of vitamin D_3 100000 IU or placebo	INT: 2.7 ± 2.8 PLA: 3.7 ± 5.2	INT: +0.3 PLA: −0.9
Sokol et al. (2012)	INT: 45 PLA: 45	INT: 55 ± 9.6 PLA: 56.9 ± 11.6	INT: 29.6 ± 6.2 PLA: 30.9 ± 7.6	Participants with CAD and vitamin D deficiency	12 weeks	ergocalciferol 50000 IU/week	[a]INT: 2.6 (5.2) PLA: 1.8 (3.5)	[a]INT: −0.17 PLA: −0.05

IL = interleukin, CRP = C-reactive protein, N = number of participants, Δ = change, INT = intervention, CNT = control, PLA = placebo, CA = calcium carbonate, 25(OH)D = 25-hydroxyvitamin D, T2DM = type 2 diabetes, PAD = peripheral artery disease, CAD = coronary artery disease. ^ = All values are means (± standard deviation (SD)). a = median (interquartile range); b = mean (95% confidence interval (CI)). Change data are defined as the follow-up minus the baseline value. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 8
Z-scores in pairwise comparison of IL-6 decrease across compounds.

	ARBs	Omega-3	Probiotic	Resveratrol	Vitamin D
ARBs		−1.501	1.543	−1.231	**−2.025**
(P-value)		(0.133)	(0.123)	(0.218)	**(0.043)**
Omega-3			**2.797**	−0.155	−1.029
(P-value)			**(0.005)**	(0.877)	(0.303)
Probiotic				**−2.467**	**−3.134**
(P-value)				**(0.014)**	**(0.002)**
Resveratrol					−0.546
(P-value)					(0.585)
Vitamin D					
(P-value)					

Significant differences ($p < 0.05$) are in bold. Negative z-scores indicate the compound on the left margin produced greater mean decreases compared with the compound on the top margin.

pathway, could relieve inflammatory processes (Calder, 2015). Indeed, we found that omega-3 produce a small but significant reduction in both IL-6 and CRP. In line with our findings, three recent systematic reviews identified omega-3 supplementation as one of the most promising treatments targeting inflammation in older adults. The reviews by Molfino et al. (2014) and Ticinesi et al. (2016), however, did not focus on a population with chronic LGI and additionally, the results were from critically ill patients in which omega-3 was administered intravenously. Another meta-analysis by Li et al. (2014) confirmed the effectiveness of omega-3, highlighting that higher reduction of IL-6 and CRP levels can be achieved in chronic non-autoimmune diseases (IL-6: −0.22 pg/ml, CRP: −0.20 mg/L). Evidence of efficacy in healthy participants, however, are still inconsistent (Li et al., 2014; Rangel-Huerta et al., 2012). Interestingly, our findings indicate that the IL-6 lowering effect is directly proportional to the duration of omega-3 treatment. This finding, together with the safety and tolerability of this compound, should encourage a long-term use of n-3 polyunsaturated fatty acids (PUFAs) in primary prevention among middle-age and older adults with chronic LGI. Fortunately, such a trial is under way and results from the ENRGISE (Enabling Reduction of low-Grade Inflammation in SEniors) trial should be reported in approximately one year (Manini et al., 2017).

Probiotics are food supplements that contain live microorganisms such as *Bifidobacteria* and *Lactobacilli*. The rationale of probiotic intervention in inflammaging is built on the evidence that age–related changes in human gut microbiota composition (from fermentative to putrefactive bacterial flora) (Lakshminarayanan et al., 2014) could be related with elevated inflammatory markers and other geriatric conditions (e.g. frailty (Claesson et al., 2012), sarcopenia (Rampelli et al.,

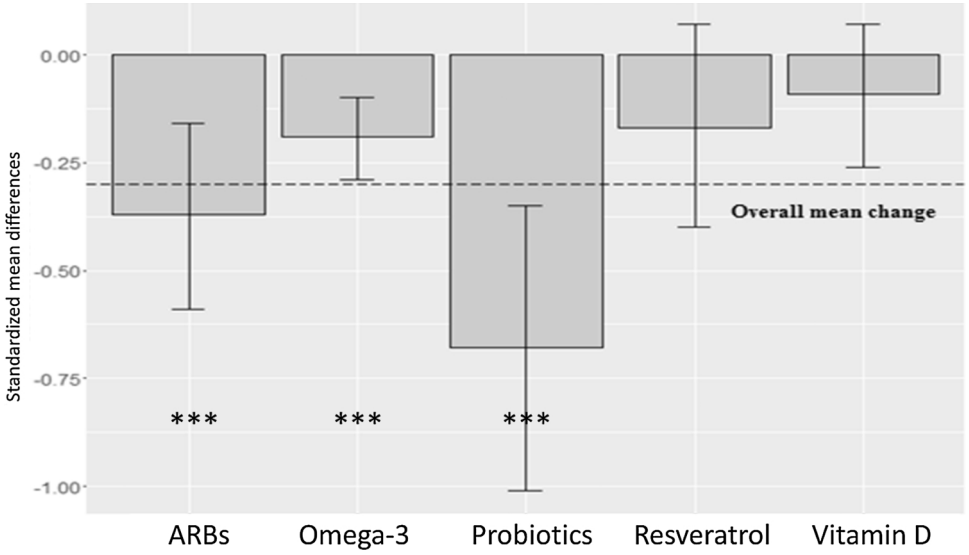

Fig. 5. Mean decrease in IL-6 by compound. Values are given as standardized mean difference (SMD) and 95% confidence interval (CI). Dashed line shows mean change of all compounds. P-values compared to placebo/control groups = *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

Table 9
Z-score in pairwise comparison of CRP decrease across compounds.

	ARBs	Metformin	Omega-3	Probiotics	Resveratrol	Vitamin D
ARBs		−0.400	−0.289	1.234	0.367	−1.244
(P-value)		(0.689)	(0.773)	(0.217)	(0.714)	(0.213)
Metformin			0.183	1.645	0.651	−1.436
(P-value)			(0.855)	(0.100)	(0.515)	(0.151)
Omega-3				1.562	0.583	−1.466
(P-value)				(0.118)	(0.560)	(0.143)
Probiotic					−0.693	**−2.151**
(P-value)					(0.488)	**(0.031)**
Resveratrol						−1.188
(P-value)						(0.235)
Vitamin D						
(P-value)						

Significant differences ($p < 0.05$) are in bold. Negative z-scores indicate the compound on the left margin produced greater mean decreases compared with the compound on the top margin.

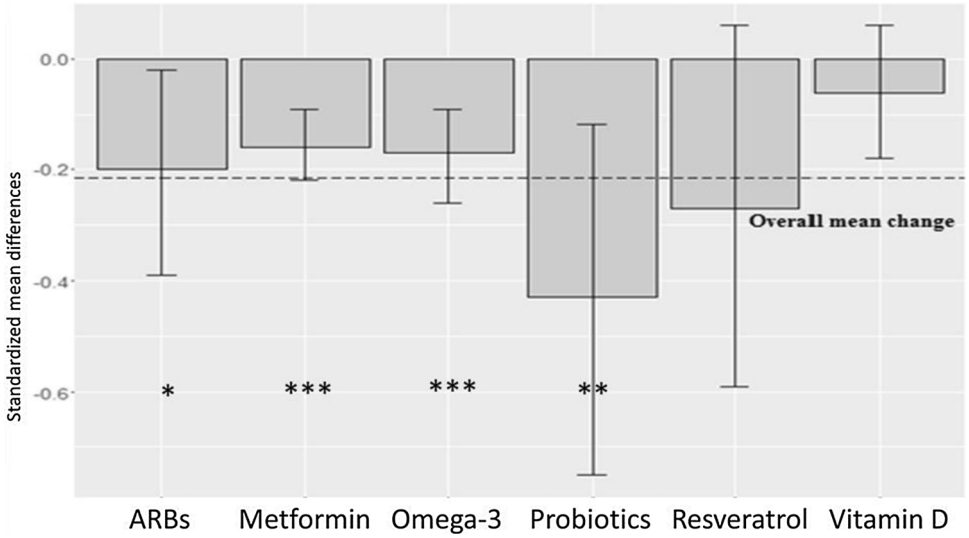

Fig. 6. Mean decrease in CRP by compound. Values are given as standardized mean difference (SMD) and 95% confidence interval (CI). Dashed line shows mean change of all compounds. P-values compared to placebo/control groups = *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$.

2013), cognitive impairment and AD (Porter et al., 2000; Widner et al., 1999)) by reduced production of short-chain fatty acids (SCFAs) which have a powerful immunoregulatory activity (Shapiro et al., 2014). Probiotics have the potential to rebalance gut microbiota and modulate gut immune response inhibiting the NF-κB pathway (Kim et al., 2012). Our findings suggest a significant moderate to large effect size of probiotics supplementation on reduction of inflammatory biomarkers, but it should be considered that this result could be overestimated by a significant small-study effect, at least for IL-6 studies. We also showed longer treatment durations were associated with greater reductions in IL-6. A recent meta-analysis by Mazidi et al. (2017) reported a significant reduction of serum CRP (−1.35 mg/L) following probiotics supplementation. However, the 20 RCTs that they included had mean age ranging from 6 months to 85 years, some of them had short follow-up (7 days), and also involved participants with acute inflammation. Other meta-analyses on patients with T2DM did not support a significant effect of probiotics on IL-6 and CRP levels (Samah et al., 2016; Yao et al., 2017). Perhaps the anti-inflammatory action of probiotics is stronger in specific conditions (i.e., acute disease or chronic LGI compared to others) or is dependent on the strain of microorganisms. Further research is needed to elucidate these aspects.

Another important finding of our meta-analysis was that resveratrol did not show a significant effect on IL-6 and CRP levels in chronic LGI. For resveratrol, our results are in line with those of a previous meta-analysis in which intervention did not lead to any significant reduction of CRP levels (Sahebkar et al., 2015). Interestingly, Timmers et al. (2011) demonstrated that 30 days of resveratrol supplementation induces metabolic changes in obese humans, mimicking the effects of caloric restriction, but they did not find any relation with IL-6 levels. Considering the relatively small sample size of studies included in the present review, larger clinical trials should be encouraged to draw definitive conclusions about the efficacy of resveratrol in chronic systemic inflammation.

Additionally, vitamin D did not show significant effects on either IL-6 or CRP levels. Our findings are in contrast with results of a previous meta-analysis by Chen et al. (2014) that reported a reduction of CRP levels by 1.08 mg/L after vitamin D supplementation, with a more pronounced effect in the subgroup with baseline CRP ≥5 mg/L (−2.21 mg/L). However, they included RCTs carried out in a younger population and in participants with acute inflammation as defined by CRP levels > 10 mg/L. Two different systematic reviews are consistent with our findings, and they concluded that evidence of a relationship between vitamin D supplementation and inflammatory biomarkers are still weak in human studies (Chagas et al., 2012; Ticinesi et al., 2016).

4.1. Strengths and limitations

To our knowledge, this is the first meta-analysis summarizing the associations of promising nutritional and pharmacological compounds on well accepted inflammatory biomarkers (IL-6 and CRP). The six compounds examined in this meta-analysis were chosen among a broad range of compounds with anti-inflammatory properties because they met criteria representing promising, safe, tolerable, affordable and acceptable strategies for reducing chronic LGI in middle-age and older adults. This distinguishes our findings from those of other systematic reviews that included populations with acute inflammatory conditions (Chen et al., 2014; Mazidi et al., 2017; Molfino et al., 2014; Takagi et al., 2013; Ticinesi et al., 2016). Furthermore, we included only studies with a RCT design to ensure higher quality of the effects.

This review has also some limitations. First, none of the included studies were specifically designed to treat individuals with chronic LGI; this could explain the wide heterogeneity observed across the studies despite of the strict inclusion/exclusion criteria. Second, several studies had relatively small sample sizes that could potentially lead to overestimation of treatment effects. Nevertheless, we performed sensitivity analysis excluding the studies at higher risk of publication bias, and we did not detect any significant change in the results. Third, for most of the studies the assessment of chronic LGI was based only on a single baseline value which could lead to a false positive indication of an inflammatory state. Fourth, we did not investigate the “gray literature”, therefore there could be studies not published for negative outcomes that could change the magnitude of effects. Fifth, the majority of the included trials were carried out in strict population subgroups (e.g., hypertensive, diabetic, hyperlipidemic) and with different dosage of compounds, so we are unable to generalize the effectiveness in people with chronic LGI. Finally, the assays for biochemical measurements of serum IL-6 and CRP varied across studies.

4.2. Clinical perspective

In clinical practice, the presence of multiple comorbidities as infections, diabetes, hypertension, obesity, hyperlipidemia, smoking, among others are common in patients, all of which are potential causes or contributors to the chronic inflammatory state.

Since the decline in functional status and development of sarcopenia in older adults frequently correlates with elevated levels of IL-6 and

other inflammatory cytokines (Cesari et al., 2004; Ferrucci et al., 1999), the clinical assessment of functional status may be an indirect way of identifying the presence of an elevated inflammatory state.

Accumulating evidence also indicates that lifestyle changes involving caloric restriction and/or intermittent fasting may increase health span and longevity through a modulation of reactive oxygen species and inflammatory cytokines (Anton and Leeuwenburgh, 2013; Lee and Longo, 2011). Although diet represents a modifiable factor, these approaches typically require high levels of compliance that are difficult to achieve for most individuals. The traditional Mediterranean diet, which provides high amounts of n-3 PUFAs and polyphenols (typically lacking in modern Western diets) has been found to reduce inflammatory biomarkers (e.g. IL-6, TNF-α) independent of caloric restriction or weight loss (Hermsdorff et al., 2009).

The anti-inflammatory mechanisms of action of some of these compounds, as well as development of new medications designed to preserve muscle function are of interest. Some examples include: ARBs, which are often used as second line therapy for hypertension, renal protection activity and prevention of cardiac remodeling in congestive heart failure; metformin, a medication with proven value in diabetes especially in the setting of obesity, weight reduction without hypoglycemic risks; and omega-3, a natural compound with potential to reduce cardiovascular risk factors. Although this review did not find evidence of benefit from vitamin D supplementation for reducing levels of IL-6 or CRP, vitamin D deficiency has been associated with reduction in muscular strength and increased risk of falls, especially in elderly patients with concomitant polypharmacy.

The data generated by this review, through better understanding mechanisms of action of new and current medications, could be a foundation for their potential use as treatments reducing functional decline during aging. In clinical practice, it is also important to convey to patients that many of the readily available supplements have not been carefully evaluated in terms of their potential risks or even contraindications with some medications.

5. Conclusion

In conclusion, our findings provide support for the potential of ARBs, metformin, omega-3 fatty acids and probiotics to significantly reduce established biomarkers of systemic inflammation in middle-age and older adults with chronic LGI. Resveratrol and vitamin D, however, were not found to be effective in reducing markers of systemic inflammation in clinical trials conducted to date.

Ultimately, practical nutritional and pharmacological interventions targeting inflammaging that are safe, affordable, and acceptable could represent new therapeutic opportunities toward the promotion of successful aging in the near future.

6. Future directions

More studies are needed to better define the reference range of inflammatory biomarkers (e.g. IL-6, CRP) for chronic LGI. At the same time, larger RCTs targeting older adults with chronic LGI should be encouraged to clarify the relation between anti-inflammatory activity of these compounds and age-related pathologies. Specifically, future studies should test if compounds that reduce systemic inflammation can avert the decline in mobility and physical function that typically occurs among older adults.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.arr.2018.05.004.

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