The effects of ageing, BMI and physical activity on blood IL-15 levels

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The effects of ageing, BMI and physical activity on blood IL-15 levels: A Systematic Review and Meta-analyses.

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Abstract:	Aim The purpose of the study was to test the effect of ageing and physical activity on IL-15 blood concentration by meta-analyses of the literature. Methods The search was performed in PubMed/MEDLINE, Web of Science, ProQuest, Embase and Cochrane databases. First meta-analysis compared blood IL-15 of healthy adults across three age groups (<35 years, 35-65 years, and >65 years); the second compared IL-15 levels between physically active and non-physically active individuals; the third tested the effect of exercise interventions on blood IL-15 levels on participants of any age, sex, and health condition. Results From 2582 studies retrieved, 67 were selected for the three meta-analyses (age effect: 59; physical activity cross-sectional effect: 5; exercise training effect: 14). Older adults had lower blood IL-15 than young and middle-aged adults (5.30 pg/ml [4.76; 5.83]; 7.11 pg/ml [6.33; 7.88]; 7.10 pg/ml [5.55; 8.65], respectively). However, the subgroup of overweight older adults had higher IL-15 than young and middle aged overweight adults; Habitual physical activity did not affect blood IL-15 (standardized mean difference [SMD] 0.61 [-0.65; 1.88], p=0.34); Exercise intervention reduced blood IL-15 in short-term interventions (<16 weeks) (SMD -0.14 [-0.27; -0.01], p=0.04), but not studies of more than 16 weeks of intervention (SMD 0.44 [-0.26; 1.15], p=0.22). Conclusion The present meta-analyses highlight the complex interaction of age, BMI and physical activity on blood IL-15 and emphasize the need to take these factors into account when considering the role of this myokine in health throughout life.
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Dear Editor and reviewers,

We thank you for spending your time in the evaluation of our manuscript. We have revised our manuscript with changes marked in yellow and our detailed response to each comment is described below.

We are looking forward to your response.

Yours sincerely

Reviewer #1: The present review manuscript is very well write and can be accepted after major review.
Major review

1) Many times the authors write "exercise", "physical activity", or "physical exercise". I understand that these term sound similar, but are differences between their. Please, explain about and adopt just one term.

Authors' reply: Thanks for the comment, we reviewed the use of the different terms, but adopt just one of them would not be possible since we really meant two different types: one meta-analysis was about physical activity effect of IL-15 and the other exercise training interventions. We opted to use chronic exercise interventions (and we deleted all the physical exercise terms), since this term suggests a repetition of more than one exercise session, and we used physically active individuals to reinforce we were talking about groups already trained in cross-sectional studies.

2) The BMI is highlight in title, but not in the aims. Why?

Authors' reply: Thank you for noticing, it should be more clearly included in the first aim. In the beginning of our plan of analysis BMI was just a confounding factor, but since we noticed a very important effect of this variable on IL-15, we opted to give higher importance to it across the manuscript. Now we added it to our first aim.

3) IL-15 exhibit impact to visceral and subcutaneous adipose tissue depots or just in visceral adipose tissue depot? Please, explain about heterogeneous adipose tissue response from IL-15.

Authors' reply: Previously, we did not give much attention to this heterogeneity, and we really appreciate the suggestion, because we found it could be another explanation to our surprising findings. We added the possible influence of these different associations in the 3rd paragraph of the discussion.

4) Explain about differences between the cardiorespiratory capacity and physical activity level, because not similar parameters. A subject might exhibit a higher cardiorespiratory capacity and low physical activity level, or inverse.

Authors' reply: We added a sentence in the discussion of the second meta-analysis explaining the limitation of the use of different ways to access physical activity that could be not a good representation of physical activity but rather differentiate only cardiorespiratory fitness.

Highlights

- IL-15 is an anti-inflammatory myokine that has important metabolic actions such as skeletal muscle anabolism and fat reduction
- Older adults have lower blood IL-15 than young and middle-aged adults
- Within overweight individuals, older adults have higher blood IL-15 than young and middle-aged adults
- There is no consensus about habitual physical activity modulating blood IL-15 levels
- Exercise reduces blood IL-15 in interventions of less than 16 weeks, but not in interventions longer than 16 weeks

The effects of ageing, BMI and physical activity on blood IL-15 levels: A Systematic Review and Meta-analyses.

Abstract

Aim: The purpose of the study was to test the effect of ageing and physical activity on IL-15 blood concentration by meta-analyses of the literature.
Methods: The search was performed in PubMed/MEDLINE, Web of Science, ProQuest, Embase and Cochrane databases. First meta-analysis compared blood IL-15 of healthy adults across three age groups (<35 years, 35-65 years, and >65 years); the second compared IL-15 levels between physically active and non-physically active individuals (cross-sectional studies); the third tested the effect of chronic exercise interventions on blood IL-15 levels on participants of any age, sex, and health condition.
Results: From 2582 studies retrieved, 67 were selected for the three meta-analyses (age effect: 59; physical activity cross-sectional effect: 5; exercise training effect: 14). Older adults had lower blood IL-15 than young and middle-aged adults (5.30 pg/ml [4.76; 5.83]; 7.11 pg/ml [6.33; 7.88]; 7.10 pg/ml [5.55; 8.65], respectively). However, the subgroup of overweight older adults had higher IL-15 than young and middle aged overweight adults; Habitual physical activity did not affect blood IL-15 (standardized mean difference [SMD] 0.61 [-0.65; 1.88], p=0.34); Chronic exercise reduced blood IL-15 in short-term interventions (<16 weeks) (SMD -0.14 [-0.27; -0.01], p=0.04), but not studies of more than 16 weeks of intervention (SMD 0.44 [-0.26; 1.15], p=0.22).
Conclusion: The present meta-analyses highlight the complex interaction of age, BMI and physical activity on blood IL-15 and emphasize the need to take these factors into account when considering the role of this myokine in health throughout life.

Keywords: Aging; Interleukin-15; Exercise; Physical activity; Exercise therapy; BMI.

Introduction

The cytokine IL-15 is mainly produced by monocytes and macrophages in response to pathogens and has immunoregulatory effects on a variety of immune cells including the activation of NK cells and T lymphocytes and induction of cytokine production by neutrophils and monocytes (1,2). It is also highly expressed in skeletal muscle (3–5) and thus has also been classified as a myokine with effects on many other tissues such as brain (6), bone (7), skeletal muscle (4,8) and adipose tissue (3). IL-15 has important metabolic actions, stimulating skeletal muscle anabolism and protecting against the negative effects of visceral adiposity (3,4,8,9). Specifically, IL-15 stimulates differentiated myocytes and muscle fibres to increase their contractile protein content and inhibit degradation of muscle proteins contributing to hypertrophy (8,9). IL-15 is the most abundant cytokine in skeletal muscle (10) and the levels of IL-15 in muscle are among the highest of any tissue (11), suggesting muscle activity might be an important regulator of its expression and biological function. IL-15 also prevents lipid deposition in pre-adipocytes and increases glucose uptake by muscle, potentially ameliorating the deleterious effects of white adipose tissue (3,12,13). These effects may, for example, help to prevent fat accumulation in the thymus with aging which leads to thymic atrophy and reduced production of naïve T cells with impact on immunity (14).

As such IL-15 has been proposed as a positive modulator of aging trajectory and age-related diseases such as sarcopenia and diabetes as well as obesity (12,15). Although some studies have shown blood concentrations of IL-15 to be significantly lower in older adults compared to young individuals (16,17), other studies do not report age differences (18,19). One confounding factor among these studies might be the participants differing health status, since some diseases and obesity appear to alter IL-15 in different ways (20–22). Thus, one aim of the present study was to confirm by meta-analysis of the current literature whether advancing age reduces blood IL-15 levels in healthy subjects, also considering the influence of BMI on ageing effects.

Chronic exercise is a potential anti-inflammatory therapy to delay or reduce the age-related increase in systemic inflammation, termed inflammageing (23,24). Different of chronic exercise interventions that involved systematic exercise, physical activity “any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level” (25), and few studies have also tested associations between physical activity and blood IL-15 concentrations. Higher IL-15 in physically active individuals has been reported in cross-sectional studies (26,27), though this is not a universal finding (22). Furthermore, interventional studies have shown more contradictory results, with exercise leading to increase (28), no change (29), and even a reduction (30) of blood IL-15. This lack of consensus may be due to the different health condition among subjects, or the variety of exercise protocols tested. In this way, the additional aims of this study were related to the potential of exercise to regulate blood IL-15 concentration. Specifically, we aimed to test the difference between blood IL-15 concentrations in physically active and non-physically active individuals, and to test blood IL-15 before and after chronic exercise interventions, by meta-analysis of the existing literature.

Methods

A systematic search was performed on PubMed, Web of Science, ProQuest, Embase, and Cochrane databases in January 2021. First, the PubMed syntax was exhaustively tested and rebuilt until approved by all reviewers as the following format: *("Aged" [mh] OR "Aging" [mh] OR "Aged 80 and over" [tiab] OR "Frail Elderly" [mh] OR "old" [tiab] OR "ancient" [tiab] OR "old-aged" [tiab] OR "elder" [tiab] OR "aged 60 and over" [tiab] OR "age" OR "year") AND ("Interleukin-15" [mh] OR "IL-15" [tiab] OR "IL15"[tiab] OR "Interleukin 15"[tiab]) AND ("english"[Language] OR "Portuguese"[Language]) NOT ("review"[publication type]).* Then, other equivalent searches were planned for each of the other databases (Table S1).

The selection of studies by their abstracts was made on Rayyan (31). The studies retrieved after this selection were scrutinized in a spreadsheet and clustered for each of the 3 main analyses. Only articles in English were included and no restriction on publication date was imposed. Participants of both sexes and over 18 years of age were considered.

Mean, standard deviation (SD), sample number (n) for each time point and subgroup within studies were used to analyse the blood IL-15 concentration picogram per millilitre (pg/ml). Data not presented as mean and standard deviation (SD), were converted to mean and SD for analysis. The standard error (SE) was converted to SD by the equation $SD = SE * (\sqrt{n})$, if SD was not provided in the original study. When median and interquartile range (IQR) were reported, median was accepted as mean and SD was estimated by equation ($SD = (IQR/1.35)$)(32). When numerical data were not available, graphical data were extracted from the image pixels converted in an online software (https://apps.automeris.io/wpd/), in which the average of three recordings for each data point was used for analysis.

The first meta-analysis included studies assessing blood IL-15 concentration in healthy individuals that necessarily reported the age of their participants. The comparison between age groups considered the mean age group of each study (<35, 35-65, ≥65). When the studies did not present an average, we used the median; and in the absence of the median, we calculated the mean between the minimum and maximum age of the participants included in the study. Obese individuals were not excluded; however, the confounding effect of obesity was isolated in further subgroup analysis. Thus, all studies were divided into categories based on the mean BMI reported; being <25 (kg/m²) normal weight, 25-30 (kg/m²) overweight and >30 (kg/m²) obese.

The second meta-analysis included studies that compared blood IL-15 concentration between physically active individuals and non-physically active individuals, according to each primary study definition.

The third meta-analysis included studies assessing blood IL-15 concentration before and after a chronic exercise intervention. In this analysis participants in different health conditions were included and compared in further subgroup analysis. For this meta-analysis, characteristics of the chronic exercise intervention protocols were also extracted. We categorized the studies according to age (<64 years vs. ≥65 years), sex (men and women), exercise protocol (aerobic, strength and combined strength plus aerobic), and length of intervention (<16 weeks and ≥16 weeks). We also categorized the studies by health condition; and when the study was not designed for a specific disease population, we classified as non-specific diseases, since we could not ensure all of the individuals were healthy.

Quality of studies

Studies were not excluded based on their quality, but rather used for descriptive purpose. The Newcastle-Ottawa scale was used to assess the risk of bias regarding selection, comparability, and exposure between physically active and non-physically active groups in each study. The PEDro scale was used to assess the quality of interventional studies (33). 1: Eligibility criteria specified; 2: Random allocation; 3: Concealed allocation; 4: Groups similar at baseline (IL-15 concentration); 5: Subject blinding; 6: Instructor blinding; 7: Assessor blinding; 8: Less than 15% dropouts; 9: Intention-to-treat analysis; 10: Between-group statistical comparisons; 11: Point measures and variability data. Thus, the scores on the PEDro scale ranged from 0 (very low methodological quality) to 10 (high methodological quality). The quality of the studies was used only for qualitative purpose and was not an exclusion criterion.

Statistical analysis

The three meta-analyses were performed using the Comprehensive Meta-Analysis (CMA) software, version 3.3.070. In the first meta-analysis we calculated the raw mean difference (RMD) of circulating IL-15 (mg/ml) between groups of different age groups (<35, 35-65 and >65). In the second, we calculated the standardized mean difference (SMD) of blood IL-15 between physically active and non-physically active individuals. In the third, SMD was calculated based on the difference between pre- and post-intervention of the training group (a) or the difference in variations (pre-post) between the training group and the control group (b) for studies containing a control group. In the third meta-analysis, we also chose to use SMD, since even using the same measurement units, the studies presented very different mean and SD magnitudes that would lead to bias. Subgroups of participants within each study were treated in the analysis as they were different studies.

When there was significant heterogeneity ($p \leq 0.05$), we applied randomized effects and when there was no significant heterogeneity ($p > 0.05$) we applied fixed effects. Publication biases were analysed using the Egger test.

The first meta-analysis was based on the studies mean age (<35, 35-65 and >65) and BMI was also included as confounding factor (normal weight vs. overweight vs. obese.

Since there was substantial inconsistency (I^2>50%) in the third meta-analysis, further subgroup analyses were run for age, health condition, sex, exercise type and length of intervention. The Q test was used to identify differences between subgroup categories. The p-value ≤0.05 was considered significant for all analysis.

Evidence quality

The quality of evidence was assessed by GRADE approach, considering the evaluation items of each study. For the meta-analysis of observational studies (Comparison between IL-15 of physically active and non-physically active) starts with 2 points and one or two points are added according to effect size, dose-response gradient, and positive influence of confounding factors. Details of each quality of evidence analysis will be described in the Results section, step by step. This will lead to a quality of evidence ranging from very low (≤1) to high (4).

The quality of the evidence for the chronic exercise intervention effects on IL-15 was also assessed by GRADE approach but considering the evaluation items for interventional studies. In this type of analysis, we start with 4 points and remove one or two points according to the severity of bias in each item. It will lead to a quality of evidence that ranges from very low (≤1) to high.

Results

Figure 1 details the selection process of the studies for all meta-analyses. In the Kuczynski et al. study (34) we assumed the data presented were the interquartile range, although not described, since the distribution of IL-15 was described as non-normal and the difference between the maximum and minimum values until the mean was different; In the van der Zij et al. study (35) the control group was not considered because the IL-15 values were below the quantification level. In Chang et al. (16) two groups with participants under the age of eighteen were excluded.

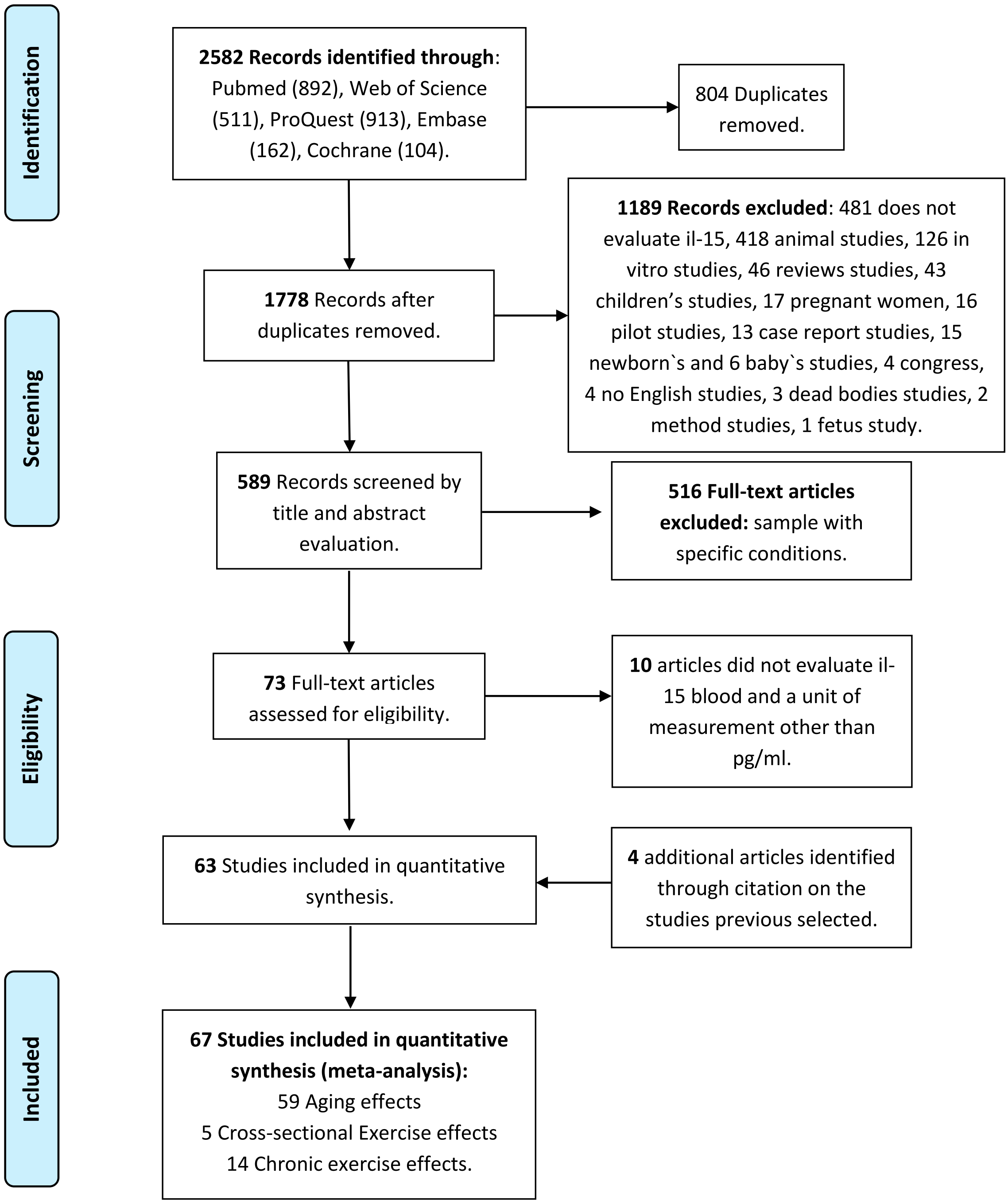

Figure 1. Flow diagram of study selection.

Older adults have lower blood IL-15 than middle aged and young adults, unless they are overweight

Table 1 shows the characteristics of the 59 studies selected to compare the concentration of IL-15 between individuals of different age groups. A hundred and two age subgroups were included in the analysis. Five studies were not included in this meta-analysis due to the different unit of measures used (36–40).

Table 2 shows that individuals >65 years have lower blood IL-15 concentrations compared to the other age groups (<35 years and 35-65). IL-15 was also affected by BMI differences, and this effect was not linearly associated with higher weight, since overweight individuals had higher blood IL-15 concentrations than normal weight or obese individuals (Table 2).

Therefore, isolating age effects within BMI subgroups, we found that lower IL-15 concentrations in older adults were not significantly different from other age categories within normal weight individuals (Table 2). However, within overweight individuals, there was a linear increase in IL-15 with age, showing older adults had significantly higher IL-15 than young adults (Table 2). Unfortunately, almost all the obese individuals were middle aged, and just one study included obese older adults, which limited the understanding of age effects within the obese population. It is noteworthy, that complementary analysis (not shown on Table 2) comparing age effects by categories based on range (without overlapping across age groups), reinforce normal weight older adults had significantly ($p = 0.011$) lower blood IL-15 (2.64 pg/ml [1.79; 3.49]) than young normal weight individuals (4.04 pg/ml [3.68; 4.40]). Within the overweight adults the analysis based on range also showed significantly higher IL-15 ($p<0.001$) for older adults (11.53 pg/ml [4.48; 18.58]) (30,41–43) than young (3.14 pg/ml [2.77; 3.51]). It is noteworthy that among the analysis of categories based on age range groups, no study was included in the middle-aged adult group and just one study included obese participants exclusively within the older adults age range.

Table 1. Characteristics of the studies included in the healthy individual analysis.

First author, year (Subgroup)	n	Sex	Age (years)	Age category	Body mass Index (kg/m²)	Body Mass Index category	IL-15 (pg/ml)
Ahn and Kim, 2020 (44) (High normal blood pressure)	12	Both	72.00 ± 3.81	>65	25.27 ± 2.53	overweight	20.93 ± 10.09
Ahn and Kim, 2020 (44) (Normal blood pressure)	18	Both	69.22 ± 4.14	>65	25.23 ± 3.87	overweight	22.39 ± 11.31
Al-Shukaili, 2013 (42)	30	Both	35.00 ± 7.00	<35	NR	NR	10.20 ± 10.30
B, 2020 (35)	65	Both	43.00 ± 11.00	35-65	38.00 ± 5.00	obese	10.30 ± 18.80
Bartlett and Duggal, 2020 (26) (Heathy)	25	Both	67.04 ± 5.97	>65	25.14 ± 3.90	overweight	34.92 ± 7.29
Bartlett and Duggal, 2020 (26) (Sedentary)	25	Both	63.36 ± 4.42	35-65	28.70 ± 4.56	overweight	7.23 ± 9.81
Bazgir, 2015 (27) (Athletes concentric exercise)	14	Men	24.10 ± 2.50	<35	23.80 ± 2.10	normal weight	1.79 ± 0.60
Bazgir, 2015 (27) (Athletes eccentric exercise)	14	Men	24.10 ± 2.50	<35	23.80 ± 2.10	normal weight	1.72 ± 0.40
Bazgir, 2015 (27) (Non-athletes)	14	Men	20.80 ± 2.30	<35	21.60 ± 2.60	normal weight	1.43 ± 0.17
Beavers, 2010 (30) (Training)	182	Both	76.40 ± 4.10	>65	30.70 ± 6.00	obese	1.77 ± 0.56
Beavers, 2010 (30) (Control)	186	Both	77.0 ± 4.40	>65	29.80 ± 5.50	overweight	1.76 ± 0.42
Biancotto, 2013 (43)	144	Both	41.50 ± 20.50	<35	NR	NR	76.08 ± 161.04

Bowman, 2018 (45)	102	Both	69.80 ± 7.70	>65	NR	NR	3.00 ± 0.60
Brunelli, 2015 (28) (Control)	17	Men	48.00 ± 1.72	35-65	31.01 ± 3.06	obese	0.78 ± 0.16
Brunelli, 2015 (28) (Training)	13	Men	49.29 ± 1.31	35-65	30.95 ± 0.40	obese	0.45 ± 0.07
Bugera, 2018 (46)	10	Men	25.78 ± 3.56	<35	25.93 ± 2.22	overweight	0.78 ± 0.69
Cassano, 2017 (47)	118	Both	42.10 ± 13.10	35-65	24.99 ± 4.10	normal weight	4.12 ± 8.44
Chang, 2016 (16) (20-39y)	40	Both	30.0 ± 0.80	<35	NR	NR	55.94 ± 5.85
Chang, 2016 (16) (40-59y)	48	Both	51.10 ± 0.80	35-65	NR	NR	56.21 ± 8.21
Chang, 2016 (16) (60-79y)	31	Both	68.3 ± 5.10	>65	NR	NR	37.37 ± 6.04
Choe, 2013 (48)	40	Both	55.40 ± 12.80	35-65	NR	NR	10.40 ± 0.90
Christiansen, 2013 (49) (Men)	16	Men	33.00 ± 11.00	<35	27.60 ± 6.00	overweight	7.00 ± 12.85
Christiansen, 2013 (49) (Women)	15	Women	41.10 ± 6.00	35-65	26.90 ± 5.00	overweight	6.40 ± 6.32
Christiansen, 2013 (49) (Normal weight)	15	Both	32.70 ± 12.00	<35	22.40 ± 2.00	normal weight	7.90 ± 8.39
Christiansen, 2013 (49) (Overweight/ Obese)	16	Both	41.30 ± 4.00	35-65	31.80 ± 3.00	obese	3.40 ± 8.16
Csencsits-Smith, 2016 (50)	15	Both	56.80 ± 9.20	35-65	27.30 ±	overweight	6.33 ± 9.68
Di Renzo, 2010 (51) (Normal weight)	20	Women	27.50 ± 7.50	<35	19.20 ± 6.48	normal weight	4.01 ± 5.00
Di Renzo, 2010 (51) (Obese)	20	Women	27.6 ± 7.40	<35	27.89 ± 20.34	overweight	6.94 ± 7.96
Di Renzo, 2010 (51) (Normal weight)	20	Women	27.70 ± 7.30	<35	22.64 ± 8.09	normal weight	6.64 ± 5.60
Duggal, 2018 (17) (Old)	65	Both	68.50 ± 11.50	>65	NR	NR	10.76 ± 16.09

Duggal, 2018 (17) (Young)	52	Both	28.00 ± 8.00	<35	NR	NR	21.58 ± 41.09
Duggal, 2018 (17) (Masters)	119	Both	67.00 ± 12.00	>65	NR	NR	29.50 ± 57.02
Gangemi, 2005 (19) (>95y)	30	Both	>95	>65	NR	NR	3.05 ± 1.41
Gangemi, 2005 (19) (30-59y)	21	Both	44.50 ± 14.50	35-65	NR	NR	1.73 ± 0.50
Gangemi, 2005 (19) (60-89y)	21	Both	74.50 ± 14.50	>65	NR	NR	1.94 ± 1.32
Gokkusu, 2010 (52)	162	Both	62.50 ± 12.20	35-65	20.30 ± 2.00	normal weight	1.12 ± 0.85
Gonza1ez-Reimers, 2011 (53)	13	Both	47.00 ± 9.51	35-65	NR	NR	1.69 ± 0.26
Gullick, 2013 (54)	30	Both	51.00 ± 20.00	35-65	NR	NR	28.10 ± 6.52
Hingorjo, 2018 (55) (<23 BMI)	75	Both	19.37 ± 0.63	<35	19.60 ± 1.95	normal weight	4.04 ± 1.60
Hingorjo, 2018 (55) (>23 BMI)	58	Both	19.37 ± 0.63	<35	27.70 ± 4.18	overweight	3.14 ± 1.44
Hu, 2016 (56) (Men)	45	Men	21.40 ± 1.50	<35	NR	NR	33.40 ± 11.10
Hu, 2016 (56) (Women)	11	Women	37.40 ± 1.50	35-65	NR	NR	10.60 ± 1.80
Jekarl, 2019 (57)	80	Both	70 ±	>65	NR	NR	10.35 ± 12.49
Johansson, 2017 (58)	18	Both	76 ±	>65	23.70 ± 1.85	normal weight	1.91 ± 0.43
Joy, 2016 (59) (Treatment)	11	Men	28.00 ± 5.00	<35	NR	NR	2.21 ± 0.49
Joy, 2016 (59) (Placebo)	14	Men	28.00 ± 5.00	<35	NR	NR	2.15 ± 0.48
Kakumu, 1997 (60)	10	Both	64 ±	35-65	NR	NR	6.70 ± 6.30
Knuiman, 2018 (61)	13	Men	21.20 ± 0.50	<35	22.00 ± 0.20	normal weight	3.21 ± 0.97
Kuczynski, 2005 (34)	22	Both	29.00 ± 4.00	<35	NR	NR	2.90 ± 3.33
Lambert, 2004 (62) (Placebo)	6	Men	64.00 ± 5.30	35-65	21.20 ± 2.90	normal weight	2.02 ± 0.95
Lambert, 2004 (62) (Treatment)	6	Men	66.60 ± 3.70	>65	24.30 ± 1.80	normal weight	1.84 ± 0.68

Lambert, 2004 (62) (Placebo)	5	Men	67.00 ± 6.10	>65	22.50 ± 2.80	normal weight	2.02 ± 0.29
Lambert, 2004 (62) (Treatment)	8	Men	66.90 ± 5.50	>65	22.90 ± 2.90	normal weight	2.26 ± 0.50
Lesiak, 2016 (63)	29	Men	51.80 ±	35-65	NR	NR	4.88 ± 0.60
Levinger, 2016 (38)	10	Both	67.40 ± 2.40	>65	28.20 ± 1.70	overweight	31.52 ± 5.00
Lis, 2015 (64) (Athlete with gluten)	13	Both	32.00 ± 7.00	<35	NR	NR	15.17 ± 11.94
Lis, 2015 (64) (Gluten-free athlete)	13	Both	32.00 ± 7.00	<35	NR	NR	12.65 ± 9.98
Luna, 2011 (65) (Training)	11	Men	40.40 ± 7.90	35-65	NR	NR	9.95 ± 79.48
Luna, 2011 (65) (placebo)	14	Men	40.40 ± 7.90	35-65	NR	NR	3.20 ± 14.80
Martinez-Hernandez, 2012 (66)	8	Both	47.10 ± 12.90	35-65	25.20 ± 3.60	overweight	1.75 ± 0.41
Micielska, 2019 (67) (Control)	13	Women	45.00 ± 13.00	35-65	NR	NR	3.29 ± 3.28
Micielska, 2019 (67) (Training)	20	Women	40.00 ± 11.00	35-65	NR	NR	3.98 ± 4.07
Michel Rentzos, 2007 (68)	15	Both	70.00 ± 8.00	>65	NR	NR	2.0 ± 0.22
M Rentzos, 2007 (69)	19	Both	65.8 ± 11.2	>65	NR	NR	3.0 ± 0.44
Minuzzi, 2019 (18) (Masters)	20	Both	53.10 ± 8.80	35-65	25.10 ± 4.60	overweight	24.32 ± 9.66
Minuzzi, 2019 (18) (Young)	9	Both	31.80 ± 3.00	<35	21.80 ± 2.00	normal weight	1.71 ± 2.16
Minuzzi, 2019 (18) (Old)	10	Both	54.20 ± 5.90	35-65	24.30 ± 3.20	normal weight	2.97 ± 3.98
Mustafa, 2015 (70)	23	Both	28.00 ±	<35	NR	NR	0.00 ± 9.40
Nathella, 2017 (71)	66	Both	41.00 ± 19.00	35-65	NR	NR	5.05 ± 6.74
Nishida, 2014 (72) (Men)	737	Men	57.30 ± 8.10	35-65	23.90 ± 2.90	normal weight	11.73 ± 1.42

Nishida, 2014 (72) (Women)	1838	Women	56.30 ± 8.10	35-65	22.60 ± 3.10	normal weight	11.49 ± 1.49
Nishida, 2015 (73) (Training)	31	Both	70.40 ± 5.80	>65	24.20 ± 3.70	normal weight	2.91 ± 0.50
Nishida, 2015 (73) (Control)	31	Both	69.70 ± 6.60	>65	22.50 ± 2.50	normal weight	3.36 ± 3.11
Notarnicola, 2015 (74)	19	Both	45.80 ± 1.80	35-65	NR	NR	0.41 ± 2.96
Oliver, 2016 (40)	10	Both	27.00 ± 4.00	<35	NR	NR	1.06 ± 0.23
Olszewski, 2001 (75)	20	Both	25.00 ± 3.00	<35	NR	NR	0.30 ± 0.01
Pérez-López, 2018 (22) (Lean physical activity)	25	Both	46.00 ± 4.10	35-65	23.90 ± 3.10	normal weight	1.85 ± 0.40
Pérez-López, 2018 (22) (Lean non-physically active)	28	Both	47.00 ± 3.90	35-65	24.20 ± 3.50	normal weight	2.70 ± 0.50
Pérez-López, 2018 (22) (Obese physical active)	64	Both	44.40 ± 8.80	35-65	37.40 ± 4.70	obese	2.50 ± 0.60
Pérez-López, 2018 (22) (Obese non-physically active)	79	Both	44.30 ± 8.10	35-65	38.0 ± 6.00	obese	3.30 ± 0.70
Phenekos, 2004 (76)	25	Both	52.30 ± 12.80	35-65	NR	normal weight	2.03 ± 0.18
Prestes, 2009 (29)	35	Women	63.18 ± 4.8	35-65	NR	normal weight	31.38 ± 70.16
Ragino, 2020 (77)	50	Both	35.00 ± 6.88	<35	22.90 ± 3.40	normal weight	2.10 ± 2.37
Rinnov, 2014 (78) (Training)	10	Men	30.50 ± 5.50	<35	25.10 ± 2.10	normal weight	0.89 ± 0.66
Rinnov, 2014 (78) (Control)	5	Men	25.20 ± 3.30	<35	23.20 ± 2.40	normal weight	1.12 ± 0.31
Sánchez-Jiménez (79)	46	Both	46.30 ± 15.10	35-65	26.40 ± 4.40	overweight	4.00 ± 2.50
Shammam, 2015 (80)	70	Both	33.00 ± 7.83	<35	NR	NR	34.92 ± 9.03
Shibatomi, 2001 (81)	33	Both	44.70 ± 12.70	35-65	NR	NR	2.74 ± 1.02

Siewko, 2019 (20)	60	Both	38.50 ± 31.11	35-65	22.70 ± 13.55	normal weight	0.20 ± 2.51
Tagoma, 2019 (82)	42	Women	29.20 ± 10.70	<35	NR	NR	72.10 ± 63.55
Urzi, 2019 (55) (Control)	9	Women	88.90 ± 5.30	>65	29.10 ± 5.10	overweight	8.37 ± 3.26
Urzi, 2019 (55) (Training)	11	Women	84.40 ± 7.70	>65	28.00 ± 5.50	overweight	6.25 ± 3.14
Uzawa, 2014 (83)	20	Both	48.5 ± 23.50	35-65	NR	NR	4.42 ± 1.55
Xia, 2011 (84)	45	Both	46.60 ± 13.40	35-65	NR	NR	264.31 ± 161.73
Yalcin, 2018 (41)	80	Both	75.00 ±	>65	29.05 ± 39.00	overweight	5.10 ± 35.81
Yang, 2017 (85)	22	Both	31.10 ± 7.10	<35	NR	NR	81.76 ± 50.00
Zhu, 2016 (86)	25	Both	32.20 ± 9.04	<35	NR	NR	19.50 ± 124.95

Note: Data are presented as mean ± SD. IL-15: mean standard deviation of IL-15 in pg/ml; y: year; SD: standard deviation; NR: Not reported.

Table 2. BMI and age subgroup analysis.

Subgroup	K	N	References	Mean	LL	UL	I²	P-value (between)
Age								
<35y	33	962	(16–18,27,34,40,42,43,46,49,51,56,59,61,64,70,75,77,78,80,82,85–87)	7.11	6.33	7.88	99.58*	<0.001
35-65y	40	3.870	(16,18–20,22,26,28,29,35,47–50,52–54,56,60,62,63,65–67,71,73,76,79,81,83,84,88)	7.10	5.55	8.65	99.97*	
>65y	23	1.120	(16,17,19,26,30,41,44,45,55,57,58,62,68,73,89,90)	5.30	4.76	5.83	99.08*	
BMI								
Normal Weight	27	3.342	(18,20,22,27,47,49,51,52,58,61,62,72,73,77,78,87)	3.27	1.26	5.28	99.96*	<0.001
Overweight	17	574	(18,26,30,41,44,46,49–51,55,66,79,87)	8.28	7.04	9.52	98.27*	
Obese	7	436	(22,28,30,35,49)	2.07	1.22	2.92	99.75*	
Age within normal weight								
Young	12	259	(18,27,49,51,61,77,78,87)	2.32	1.78	2.85	96.10*	0.573
Middle-aged	9	2984	(18,20,22,47,52,62,72)	4.25	0.67	7.84	99.98*	
Older adults	6	99	(58,62,73)	2.31	1.85	2.77	92.97*	
Age within overweight								
Young	4	104	(30,44,46,55)	3.28	1.22	5.35	96.07*	0.005
Middle-aged	6	129	(26,49,50,66,79)	7.62	4.76	10.48	96.76*	
Older adults	7	341	(26,41,44,55)	14.24	5.87	22.60	99.12*	
Age within obese								
Young			-	-	-	-	-	0.427
Middle-aged	6	182	(22,28,35,49)	2.18	1.17	3.19	99.73*	
Older adults	1	254	(30)	1.77	1.69	1.85	0.00	

Note: y: years; K: number of studies; N: number of individuals; LL: lower limit; UL: upper limit; *: Significant heterogeneity (p<0.05).

No difference in blood IL-15 between physically active and non-active adults

The characteristics of the five studies (6 subgroups) comparing physically active and non-active individuals are detailed in Table 3. The level of physical activity was classified in different ways across the studies. The studies considered physically active those who undertook regular physical activity for at least six months, or had higher number of steps per day, or higher VO_2max, or had a proven specific intensity or volume of exercise in each bout or in each week.

There was no difference between blood IL-15 of physically active individuals and non-physically active individuals (Figure 2). In general, the studies showed a low risk of bias, with their quality ranging from 5 to 6 in the New Castle Ottawa scale (Table S2). We evaluated the quality of evidence as low (GRADE score=2), due to the low magnitude of difference between groups, and no clear dose-response effect or positive influence of confounding factors. Within each age category (middle aged and older adults) there was also no difference between groups (data not shown).

Table 3. Characteristics of the studies is a cross-sectional analysis.

First author, year (Subgroup)	n (CO)	Sex	Trained age (CO)	Training time	Physical activity level (CO)	Physically active BMI (kg/m²)	Control BMI (kg/m²)	Physically active IL-15 (pg/ml)	Control IL15 (pg/ml)
Bartlett, 2020 (26)	25 (25)	Both	67.04 ± 5.97 (63.36 ± 4.42)	NR	Steps day 10.500 - 15.000 (2.000 - 4.000)	25.14 ± 3.90	28.70 ± 4.56	34.92 ± 7.29	7.23 ± 9.81
Bazgir, 2015 (27)	14 (14)	Men	24.10 ± 2.50 (20.80 ± 2.30)	NR	PA > 6 months (No regular exercise)	23.80 ± 2.10	21.60 ± 2.60	1.79 ± 0.60	1.43 ± 0.17
Duggal, 2018 (17)	125 (75)	Both	67.00 ± 12.00 (68.50 ± 11.50)	NR	Cycle 60-100 km in 5.5 - 6.5 hours (Adults who did not practice regular physical activity)	NR	NR	29.50 ± 57.02	10.76 ± 16.09
Minuzzi, 2019 (18)	20 (10)	Both	53.10 ± 8.80 (54.20 ± 5.90)	24 years	VO_2max 40.33 ± 11.15 (29.29 ± 4.14)	25.10 ± 4.60	24.30 ± 3.20	24.32 ± 9.66	2.97 ± 3.98
Pérez-López, 2018 (22) (lean)	25 (28)	Both	46.00 ± 4.10 (47.00 ± 3.90)	NR	≥180 min/week (<180 min/week)	23.90 ± 3.10	24.20 ± 3.50	1.85 ± 0.40	2.70 ± 0.50
Pérez-López, 2018 (22) (obese)	64 (79)	Both	44.40 ± 8.80 (44.30 ± 8.10)	NR	≥180 min/week (<180 min/week)	37.40 ± 4.70	38.00 ± 6.00	2.50 ± 0.60	3.30 ± 0.70

Note: CO: control; NR: not reported.

First author, year (subgroup)	PA	NPA	SMD	LL	UL	p-Value	Relative weight
Bartlett, 2020	25	25	3.204	2.366	4.042	0.000	16.29
Bazgir, 2015	14	14	0.816	0.045	1.587	0.038	16.47
Duggal, 2018	125	75	0.406	0.117	0.695	0.006	17.38
Minuzzi, 2019	20	10	2.581	1.580	3.583	0.000	15.80
Perez-Lopez, 2017 (NWPA)	64	79	-1.217	-1.576	-0.859	0.000	17.29
Perez-Lopez, 2017 (OPA)	25	28	-1.865	-2.511	-1.220	0.000	16.77
Overal effect (randomized)	**273**	**231**	**0.611**	**-0.655**	**1.877**	**0.344**	**100**

Heterogenity tests: Q= 169.89; df= 5.00 p= 0.00; I^2=97.06%
Main hypothesis test: Tau^2= 1.54; Z = 0.96; p = 0.34

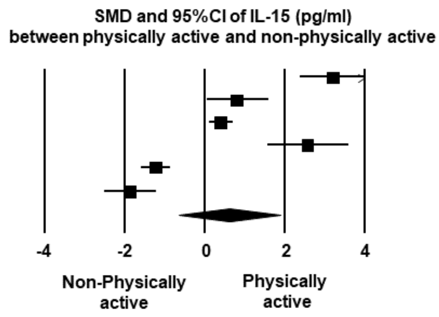

Figure 2. Forest plot of meta-analysis 2: difference between long-term trained and untrained individuals in the blood concentration of IL-15. PA: physically active; NPA: non-physically active; LL: lower limit; UL: upper limit; NWPA: normal weight physically active; OPA: obese physically active.

Effect of chronic exercise intervention on blood IL-15

Fourteen studies (18 subgroups) were included in the third meta-analysis (Table 4). Most studies included older adults, some included middle-aged participants, and only two included young participants. Most participants were female or both sexes, with only three studies including only males. Some studies have included postmenopausal women or individuals with comorbidities such as prehypertension, obesity, cancer, type 2 diabetes mellitus, mild cognitive impairment and chronic obstructive pulmonary disease. As for the chronic exercise protocols, they varied between aerobic, strength and combined, with medium to high intensities. Most studies included in this analysis presented low quality due to lack of concealed allocation of groups, blinding of participants, instructors and evaluators, high drop-out rates without intention-to-treat analysis, varying their PEDro score from 1 to 5 points (Table S3).

Figure 3 shows that chronic exercise intervention did not change the blood IL-15 concentration. The GRADE approach suggested low quality of evidence (GRADE score = 2), based on (1) high inconsistency (I^2=77.65); (2) poor quality of original studies. We did not remove any point of indirect evidence, since all tested the effects of the intervention, with most of them including a control group for comparisons, there was no publishing bias (Egger test p-value > 0.05); and no imprecision (sample size training group: 572 and sample size control group:363).

Table 5 shows the subgroup analysis of the intervention studies. Analysis of individual characteristics shows that individuals aged ≥65 years reduced the blood concentration of IL-15 with training, while younger individuals did not. The health status between healthy and unhealthy individuals and the difference between men and women are not determinants for the increase in the blood concentration of IL-15 with training (Table 5). Analysis of the characteristics of the chronic exercise interventions showed that interventions with <16 weeks duration reduced IL-15, whereas intervention ≥16 weeks did not. The weekly frequency and type of exercise protocol did not affect IL-15 concentration (Table 5).

Table 4. Characteristics of the intervention analysis studies**.**

First author, year (Subgroup)	**Age**	**Health condition**	**Sex**	**Chronic exercise group**			**Control group**			**Protocol**	**Weekly frequency**	**Length of Intervention**	**Length of Inte. category**
				IL-15 pre	**IL-15 post**	**N**	**IL-15 pre**	**IL - 15 post**	**N**				
Ahn and Kim, 2020 (41)	72.00 ± 3.81	PH	Women	20.93 ± 10.09	17.34 ± 6.82	12	22.39 ± 11.31	17.59 ± 8.75	18	CT	3	24 Weeks	>16
Banitalebi, 2019 (91) (CT)	54.14 ± 5.43	DM2	Women	3.81 ± 0.23	3.60 ± 0.25	14	3.86 ± 0.25	3.76 ± 0.29	14	CT	3	10 Weeks	<16
Banitalebi, 2019 (91) (Sprint)	55.36 ± 5.94	DM2	Women	3.94 ± 0.23	3.71 ± 0.38	14	3.86 ± 0.25	3.76 ± 0.29	14	AT	3	10 Weeks	<16
Beavers, 2010 (30)	76.40 ± 4.10	Healthy	Both	1.77 ± 0.56	1.72 ± 0.42	182	1.76 ± 0.42	1.80 ± 0.54	186	CT	2-3	24 Weeks	≥16
Brunelli, 2015 (28)	49.29 ± 1.31	OBS	Men	0.45 ± 0.07	1.17 ± 0.10	13	0.78 ± 0.16	0.55 ± 0.08	17	CT	3	24 Weeks	≥16
Gomez, 2011 (92)	50.00 ± 5.00	CA	Women	41.10 ± 25.10	32.30 ± 13.60	8	35.60 ± 10.60	55.40 ± 25.20	8	CT	3	8 Weeks	<16
Lambert, 2004 (62) (PRT)	67.00 ± 6.10	Healthy	Men	2.02 ± 0.29	2.79 ± 0.58	5	2.02 ± 0.95	2.97 ± 0.71	6	RT	3	12 Weeks	<16
Lambert, 2004 (62) (TRT)	66.90 ± 5.50	Healthy	Men	2.26 ± 0.50	2.51 ± 0.76	8	1.84 ± 0.68	2.59 ± 0.83	6	RT	3	12 Weeks	<16

Mucielska, 2019 (67)	40.00 ± 11.00	Healthy	Women	3.98 ± 4.07	3.50 ± 5.36	20	3.29 ± 3.28	3.21 ± 1.83	13	AT	3	5 Weeks	<16
Nishida, 2015 (73)	70.40 ± 5.80	Healthy	Women	NR	0.12 ± 0.62*	31	NR	-0.41 ± 3.02*	NR	CT	NR	12 Weeks	<16
Prestes, 2009 (29)	63.18 ± 4.80	PM	Women	31.38 ± 70.16	54.90 ± 198.83	35	NR	NR	NR	RT	2	16 Weeks	≥16
Riechaman, 2004 (93)	21.00 ± 2.4	Healthy	Both	1.67 ± 0.53	1.64 ± 0.55	124	NR	NR	NR	RT	3	10 Weeks	<16
Rinnov, 2014 (78)	30.50 ± 5.50	Healthy	Both	0.89 ± 0.66	1.14 ± 0.53	10	1.12 ± 0.31	1.09 ± 0.29	5	AT	5	12 Weeks	<16
Tsai, 2019 (94)	66.00 ± 7.68	MCI	Both	0.70 ± 1.48	0.62 ± 1.56	19	0.81 ± 1.52	1.74 ± 1.57	18	AT	3	16 Weeks	≥16
Tsai, 2019 (94)	65.44 ± 6.76	MCI	Both	0.30 ± 1.48	1.03 ± 1.48	18	0.81 ± 1.52	1.74 ± 1.57	18	RT	3	16 Weeks	≥16
Silva, 2018 (95) (MG)	64.88 ±11.17	COPD	Both	89.11 ± 100.30	65.80 ± 42.23	16	NR	NR	NR	RT	3	12 Weeks	<16
Silva, 2018 (95) (EG)	69.35 ± 8.97	COPD	Both	57.73 ± 33.12	42.75 ± 32.91	32	NR	NR	NR	RT	3	12 Weeks	<16
Urzi, 2019 (55)	84.40 ± 7.70	Healthy	Women	6.25 ± 3.14	7.75 ± 3.34	11	8.37 ± 3.26	8.63 ± 3.41	9	RT	3	12 Weeks	<16

Note: N: individuals number; TA: trained age; PRT: placebo resistance training; CT: combined training; TRT: testosterone resistance training; IL-15 pre: interleukin 15 pre chronic exercise intervention; IL-15 post: interleukin 15 post chronic exercise intervention; T: trained; CO: control; MG: machine group; EG: elastic group; PH: pre hypertensive; OBS: obese; CA: cancer; DM2: diabetes mellitus 2; MCI: mild Cognitive Impairment; COPD: chronic obstructive pulmonary disease; PM: post menopause; RT: resistance training; AT: aerobic training; CT: combined training; *: dates in delta of change; NR: not reported.

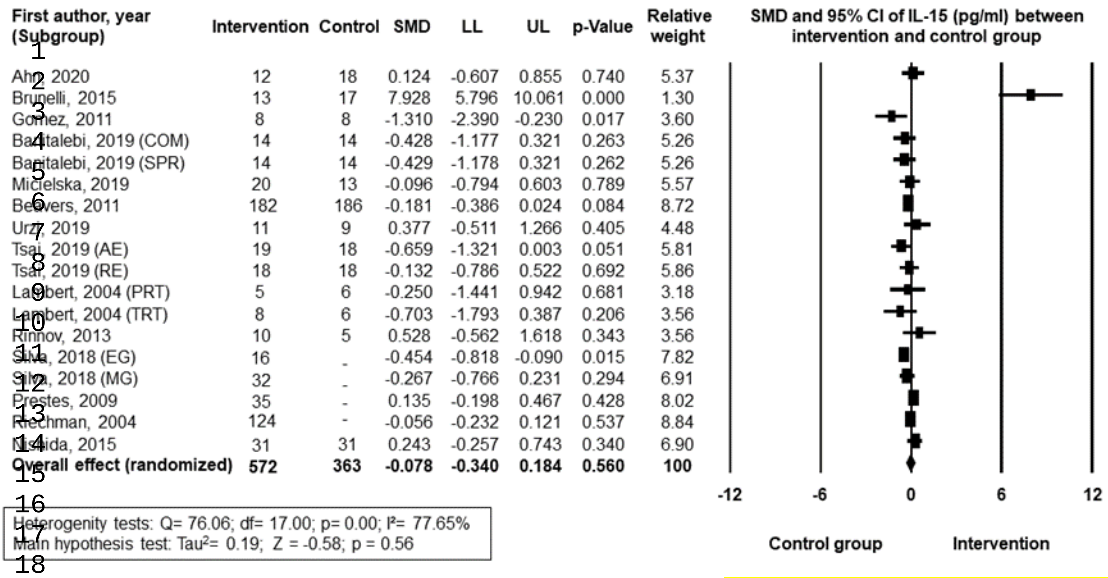

Figure 3. Forest plot of the effect of chronic exercise intervention on the IL-15 concentration. LL: lower limit; UL: upper limit; COM: combined exercise; SPR: sprint exercise; AE: aerobic exercise; RE: resistance exercise; PRT: placebo resistance training; TRT: resistance training treatment; EG: elastic group; MG: machine group.

Table 5. Subgroup analyses of the intervention with chronic exercise intervention in the blood concentration of IL-15.

Subgroups	K	N T	N CO	References	SMD	LL	UL	P-value (within)	I²	P-value (between)
Age										
<64y	9	254	71	(28,29,66,67,78,91,93,95)	0.13	-0.39	0.66	0.62	87.50%*	0.26
≥65y	9	318	292	(30,44,55,62,73,95,96)	-0.19	-0.34	-0.04	0.01	20.01%	
Health condition										
Non-specific diseases	8	391	256	(30,55,62,67,73,78,93)	-0.08	-0.20	0.04	0.21	0.00%	0.78
Specific diseases	10	181	107	(28,29,44,66,91,95,96)	0.00	-0.54	0.54	1.00	86.96%*	
Sex										
Men	3	26	29	(28,62)	2.21	-1.89	6.31	0.29	96.21%*	0.38
Women	8	145	107	(29,44,55,67,73,91,97)	0.00	-0.21	0.21	0.98	33.80%	
Type of exercise										
Aerobic	4	63	50	(67,78,91,96)	-0.29	-0.67	0.09	0.13	20.69%	0.31
Combined	6	260	274	(28,30,44,66,73,91)	0.50	-0.40	1.41	0.27	92.04%*	
Resistance	8	249	39	(29,55,62,93,95,96)	-0.10	-0.23	0.03	0.14	18.33%	
Length of intervention										
<16 wk	12	293	106	(55,62,66,67,73,78,91,93,95)	-0.14	-0.27	-0.01	0.04	29.97%	0.09
≥16 wk	6	279	257	(28–30,44,96)	0.44	-0.26	1.15	0.22	91.66%*	

Note: T: exercise trained; CO: control; K: number of studies; N: number of individuals; LL: lower limit; UL: upper limit; y: years; wk: weeks; *: Significant heterogeneity ($p<0.05$).

Discussion

The main findings of the present study were that: (1) older adults had lower circulating levels of IL-15 than young and middle-aged adults; however, the overweight subgroup of older adults have higher IL-15 than young and middle-aged overweight adults; (2) cross-sectional studies did not show significant effects of habitual physical activity on IL-15; and (3) chronic exercise intervention reduces IL-15 in subgroups of studies with less than 16 weeks of interventions and in older adults above 65 years.

Although we explored age effects on blood IL-15, we did this by an indirect subgroup analysis instead of a direct within studies comparison meta-analysis. Overall, there was significantly lower IL-15 in older adults than young and middle-aged adults in a very heterogeneous meta-analysis. This agrees with previous studies in animals (12,98). We assumed this is a negative effect of ageing, as in general IL-15 function is reported to be beneficial. For example, ultra-long-lived individuals (>95 y) have significantly higher IL-15 than young or older adults (19). Since inflammageing is highly associated with health span and life span (99), higher IL-15 in long lived individuals might be a signal of protection to reach advanced ages. It also makes biological sense as IL-15 has many effects that could be considered anti-ageing; thus, IL-15 contributes to the maintenance of naive T-cell populations by promoting survival and expansion of naive T cells, without leading to telomere shortening (17,100). Among other IL-15 roles, it has been shown to increase insulin sensitivity in animals (101), improve glucose uptake by skeletal muscle cells in vitro (2) and improve mitochondrial oxidative functions in humans (102) as well as reducing lipid synthesis in adipocytes, increasing lipid metabolism, and reducing white adipose tissue in rats (101).

The age effects observed in the overall analysis were largely comprised of studies including normal weight individuals and subgroup analysis showed that overweight older adults had higher IL-15 than overweight young and middle-aged. We speculate that the cumulative effect of being overweight over many years could lead to impaired sensitivity to IL-15, which in turn would trigger an exacerbated production to compensate, similar to what is known for insulin and leptin resistance (103–105). In fact, the effect of IL-15 on reducing white adipose tissue and improving lipid metabolism in healthy wild obese rats was abolished in leptin deficient obese mice (106). Another explanation could be a more pathological type of increase in fat mass of the younger overweight individuals, increasing mainly visceral fat (107) that is negatively associated to IL-15 concentration (3), compared to a more physiological and well distributed type of increase in fat across different tissues with ageing (108), that won`t be strongly correlated to IL-15 decrease (3). Nevertheless, the effect of obesity and ageing on IL-15 is still to be clarified, considering here obese individuals had lower IL-15 than normal weight and overweight, while overweight had higher IL-15 than normal weight individuals.

We were not able to confirm any effects of physical activity on IL-15 in the meta-analysis of these very heterogeneous cross-sectional studies. However, we noted that physically active older adults had higher IL-15 than non-physically active older adults (17,18,26); while the studies with younger individuals that are expected to have naturally higher IL-15 without physical activity (22) showed the physically active individuals had lower IL-15 than their counterparts. Indeed, Duggal et al. (17) did not find significant differences between IL-15 of healthy older adults compared to the young adults and it was the highly active master cyclists in this study that displayed higher IL-15 (17). The confounding factors such as age and BMI causing heterogeneity between studies need to be further explored in future meta-analysis, with more studies and diversified population. It is noteworthy, that the cardiorespiratory fitness, assessed by VO_2max in one study (18) does not directly represent physical activity levels, although VO_2max is improved by some types of physical activities, especially the vigorous ones (109). Likely, the higher VO_2max observed in Minuzzi et al. (18) is dependent of very higher physical activity levels in their population since they included master athletes and thus it may justify, the higher IL-15 SMD in this study.

There was also contrasting effects in the meta-analysis of chronic exercise intervention studies. In the studies with individuals above 65 years in this meta-analysis, the IL-15 was reduced after training in contrast to the effects observed in cross-sectional studies. Also, reduction of IL-15 was seen in interventions with less than 16 weeks. These findings are hard to reconcile with the high expression of IL-15 in skeletal muscle and its classification as a myokine would suggest it would increase in exercising muscle, but chronic exercise intervention does not always lead to increase in IL-15 (4,5,110) and when it occurs it seems to be pulsatile and short lasting (110).

To ensure the robustness of our results, we ran a sensitivity analysis to test chronic exercise intervention effects only in controlled studies, and it led to the same results of the analysis with all studies (SMD 0.13 [0.38; 0.64], p=0.61). The other characteristics of samples or of the interventions seemed not to influence IL-15 levels.

The effect of acute increases in IL-15 on long-term IL-15 baseline concentration remains to be confirmed (29). While some chronic aerobic exercise interventions do not affect IL-15 concentration (111), some chronic resistance exercise interventions have shown significant up-regulation of IL-15 expression (93,112). The difference between these aerobic and resistance protocols could be due to their type of muscle fibre recruited, since in general, one would expect acute resistance exercise to recruit more type II fibre than aerobic and IL-15 mRNA level is enhanced in skeletal muscles dominated by type II fibres with acute resistance exercise (4).

Perspective

The integration of previous studies with meta-analyses considerably increased our perspective on the effects of ageing and physical activity on IL-15 regulation and challenged previous notions that this anti-inflammatory cytokine would be higher in those with better health. The first new finding was that IL-15 is not consistently reduced in older adults; and, considering only overweight Individuals, IL-15 is higher in the older adults. In this way, future studies should investigate the potential of increased IL-15 as a compensatory mechanism, intended to increase muscle mass, reduce fat mass, and improve immune response, when stimulated by specific conditions such as obesity. The second unexpected finding was the reduction of IL-15 with short training interventions, that could be associated with a lower need for this compensatory mechanism. This finding also reinforced the transient nature of the IL-15 response since longer duration interventions did not change IL-15. This also highlights the need for more studies exploring the exact role of IL-15 following exercise training.

Limitations

This work has some limitations. To identify age effects on blood IL-15 we did it by subgroup analysis based on studies that did not compare defined age groups. However, the age effects were clearly similar in the two different approaches we used, considering exclusive age groups without overlap and the huge total number of studies with some overlap.

The non-linear effects of obesity on IL-15 could be caused by different percentage of muscle mass between individuals, since muscle is a major producer of IL-15; however, most studies did not report the volume of muscle mass, precluding further analysis.

Additionally, although we clarify part of exercise effects on IL-15, the quality of evidence in both cross-sectional and interventional meta-analysis were low and very low, respectively. Here, we comprehensively identified potential confounding factors of IL-15 changes with exercise, such as length of intervention, age and BMI, and future controlled studies will be necessary to confirm these findings.

Conclusion

We confirmed that older adults (> 65 years) have lower circulating IL-15 concentrations than young and middle-aged individuals; however, it seems to be an effect that occurs only in normal weight individuals. On the other hand, overweight older adults had higher IL-15 than young adults within overweight individuals. Both physical activity and chronic exercise effects on IL-15 were not confirmed by the meta-analyses, and their high heterogeneity and low quality suggest more studies will be needed to clarify the impact on IL-15. Among other potential confounding factors, the time of intervention and age of participants deserves further investigation, since we identified shorter exercise interventions and interventions in older adults reduced IL-15. Given the importance of IL-15 for muscle, immune system and adipose tissue health, understanding the effect of lifestyle factors, such as exercise and general body weight control, will be fundamental to improve interventions for older adult’s health.

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The effects of ageing, BMI and physical activity on blood IL-15 levels: A Systematic Review and Meta-analyses.

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