Profiling of proteins and targeting of myeloid mechanisms in atherosclerosis

Delfos, L.

Chapter 5

Modulation of IL-1, IL-6 and IL-18 cytokine signaling in animal models of atherosclerosis: a systematic review evaluating animal sex in preclinical research

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Abstract

Targeting of IL-1, IL-6 and IL-18 signaling is a main focus of anti-inflammatory therapy development against atherosclerosis. In preclinical atherosclerosis studies, animal sex may however affect therapeutic efficacy. Evidence for this hypothesis is lacking. We therefore aimed to study sex used and influence of animal sex on therapeutic efficacy of IL-1, IL-6 and IL-18 pathway interventions in atherosclerosis animal models. Medline (PubMed) and EMBASE (OVID) were comprehensively searched and screened to identify studies investigating the effects of targeting IL-1, IL-6 and IL-18 signaling in atherosclerosis animal models. Study characteristics and plaque size data were extracted. Individual effect sizes were calculated and pooled using the random effects model. Predefined subgroup analyses for sex were conducted. From 1744 retrieved studies, 62 papers were included in this systematic review, of which 47 papers in the meta-analyses. All 47 studies used mice, of which 41 investigated inhibitory interventions and 8 stimulatory. Meta-analyses showed a significantly smaller plaque size upon inhibition of cytokine signaling (SMD: -1.5 [-1.8 to -1.2], n=39) and a significantly larger plaque upon stimulation (SMD: 1.2 [0.3 to 2.1], n=8). The majority of the studies included male mice. Due to the limited number of studies with females, subgroup analysis for sex could only be performed for males and revealed no differences compared to the overall analyses, suggesting that male mice are suitable for such studies. More studies with female mice are required to truly assess whether animal sex is a variable in treatment efficacy of IL-1, IL-6 and IL-18 pathway interventions in atherosclerosis.

Keywords

Atherosclerosis; Preclinical studies; Inflammation; Animal sex; Outcome; Interleukin

Highlights

1. Male mice are predominantly used in atherosclerosis studies targeting IL-1, IL-6 and IL-18.
2. Inhibition of IL-1, IL-6 and IL-18 cytokine signaling reduces plaque size.
3. The number of papers using female mice in atherosclerosis studies targeting IL-1, IL-6 and IL-18 is limited.

1. Introduction

Annually, around 17.9 million people die as a result of cardiovascular diseases (CVDs), with ischemic heart disease and stroke as the most common causes (World Health Organization). The most prevalent pathology underlying many CVDs is atherosclerosis, which is caused by the buildup of lipoproteins and inflammatory cells in the vascular wall of the large arteries. Upon rupture or erosion of an atherosclerotic plaque, a vessel-occluding thrombus can be formed, causing acute cardiovascular events (ACE) (Bjorkegren & Lusis, 2022; Libby, 2021). Current treatment to reduce atherosclerosis burden is mainly aimed at lowering plasma cholesterol levels using statins or, more recently, PCSK9 inhibitors. While this has reduced the incidence of acute cardiovascular events significantly (Baigent et al., 2010; Sabatine et al., 2017), a residual inflammatory risk remains (P. M. Ridker, 2017), rendering novel insights in disease pathology and underlying mechanisms still mandatory.

To target the residual inflammatory risk, recent clinical trials focused on anti-inflammatory therapeutic strategies in high risk CVD patients. In the CANTOS trial, the therapeutic monoclonal antibody against interleukin-1β (IL-1β), canakinumab, significantly reduced the incidence of secondary cardiovascular events (P. M. Ridker et al., 2017). Colchicine, an anti-inflammatory agent (Ait-Oufella & Libby, 2024), significantly lowered the occurrence of cardiovascular events in patients with stable coronary disease in the LoDoCo trials (S. Nidorf et al., 2013; S. M. Nidorf et al., 2020). More recently, in the RESCUE trial, ziltivekimab, a therapeutic monoclonal antibody against the IL-6 ligand, reduced high-sensitivity C-reactive protein (hs-CRP) levels in patients with chronic kidney disease combined with elevated blood hs-CRP (P. Ridker et al., 2021).

These studies clearly show the clinical potential of anti-inflammatory therapeutic strategies to lower the inflammatory risk and prevent ACE, and justify further study of inflammatory mechanisms that underly atherosclerosis. Preclinical atherosclerosis models can aid in studying such mechanisms, as well as in investigating potential targets of intervention relevant for human disease. Preclinical animal models of atherosclerosis (Gisterå et al., 2022) include mouse (Ishibashi et al., 1993; Plump et al., 1992; S. Zhang et al., 1992), rabbit (Shiomi et al., 2003) and pig models (Griggs et al., 1986). Atherosclerotic mouse models are most commonly used, as mice reproduce easily and atherosclerosis develops fairly fast. Additionally, genetic modifications are relatively easy to induce. In the past decades, two widely used mouse models have been generated, being the apolipoprotein E knockout (*Apoe*$^{-/-}$) (Plump et al., 1992; S. Zhang et al., 1992) and the low-density-lipoprotein receptor knockout (*Ldlr*$^{-/-}$) (Ishibashi et al., 1993) mouse strains, both develop atherosclerosis upon hypercholesterolemia (Ishibashi et al., 1993, 1994; Plump et al., 1992; S. Zhang et al., 1992). For studies requiring a more humanized lipoprotein profile, the APOE3-Leiden mouse model or the APOE*3Leiden.CETP transgenic model (Westerterp et al., 2006) are used. These latter mouse strains show hampered clearance of apoB-containing lipoproteins and elevated triglyceride levels, and are, in contrast to the *Apoe*$^{-/-}$ or *Ldlr*$^{-/-}$ strains, responsive to lipid-lowering therapeutics such as statins (Gisterå et al., 2022; van den Maagdenberg et al., 1993). These mouse models are widely used in preclinical atherosclerosis research, but the translational potential of such preclinical studies to human disease can be hampered by strain choice and study setup, including animal sex. It is unclear whether sex of the animal affects outcome of anti-inflammatory therapy in preclinical atherosclerosis. Already in 1987, differences in atherosclerosis development in male versus female mice were reported (Paigen et al., 1987), in relation to differences in lipoprotein profiles. More recently, aged female *Ldlr*$^{-/-}$ mice were showed to have increased and altered immune cell populations in the aortic atherosclerotic plaque compared to aged male mice (Smit et al., 2024), which suggests that there may be a difference in response to inflammatory stimuli or anti-inflammatory therapy. In this systematic review, we therefore aimed to determine whether a difference in therapeutic efficacy exists between sexes of atherosclerotic animals, focusing on studies investigating interventions in the inflammatory response. We selected animal studies in which the cytokines IL-1, IL-6 and IL-18, targets of interest in recent clinical trials, were pharmacologically modulated, either via inhibitory or stimulatory strategies. The outcome of this review may contribute to the more refined design of animal experiments concerning the animal sex in preclinical atherosclerotic studies related to inflammation in atherosclerosis.

2. Methods

In this systematic review, we investigated the effects of inflammation therapeutics on plaque size in animal models of atherosclerosis, with the specific question whether therapeutic efficacy differs between male and female animals. We focused on targeting of IL-1 (including both IL-1α and IL-1β), IL-18 and IL-6 cytokine signaling. Our systematic review protocol is registered in the international prospective register of systematic reviews, PROSPERO under ID CRD42024513510, and reported following the PRISMA guidelines (Page, Moher, et al., 2021).

2.1 Search and study identification

To find the relevant papers, search strings were designed for both Medline (PubMed) and EMBASE (OVID). The complete search strings are displayed in **Supplementary Tables 1 and 2**. Literature searches were performed on November 14th, 2023.

2.2 Study selection

From the obtained records, papers occurring more than once were removed. The title and abstract of each remaining paper were screened by two independent reviewers (LD, CH, NI or IB) for the following exclusion criteria using Rayyan screening software: (1) reviews (2) human studies, (3) studies using only in vitro assays, (4) vascular remodeling models such as denudation, (partial) ligation and vein graft disease models, (5) type of study other, (6) if only non-inflammatory intervention is used, (7) commentaries, (8) case-reports, (9) protocols, (10) short communications, (11) editorial, (12) personal opinions, (13) letters, (14) posters, (15) conference abstracts, (16) dissertations, (17) thesis and graduation work, (18) other. Discrepancies were resolved by discussion with a third reviewer (LD or IB).

After the exclusion of papers based on title and abstract, the full-text document of each remaining paper was screened by two independent reviewers (LD, CH or IB) for exclusion criteria using Rayyan screening software (Ouzzani et al., 2016). These included the same criteria as for the title and abstract screening and the following additional exclusion criteria: (2) modulating molecules not being the IL-1, IL-6 and IL-18 cytokines or their receptors, (3) studies that present only genetic or epigenetic data, (4) studies that do not show atherosclerotic lesion data, (6) other exclusion criteria. In the full-text screening phase, disagreements and discrepancies were resolved by consensus after discussion with a third reviewer as well (LD or CH).

We decided post-hoc to exclude experiments (comparisons) in which genetically modified animal models were used, where the gene modification could have interfered directly with one of the investigated pathways.

Furthermore, we initially planned to assess whether the sex affects the therapeutic efficacy upon intervention. During the conduct of the systematic review we decided to post-hoc perform meta-analyses in which we determined the overall effect on plaque size for the different targets as well, mainly because no studies were available formally assessing the difference between males and females. As a consequence two criteria for exclusion that are mentioned in our protocol, are not used in practice.

2.3 Extraction of study characteristics

The following study characteristics were extracted by one reviewer (LD): author, year of publication, title, journal, language, doi, species, strain, genetic background, type of atherosclerotic model, sex, age (at disease induction, t=0), disease induction method, type of diet, cytokines, cytokine receptors, type of intervention, type of immunomodulatory component, timing intervention (relative to disease induction), timing of outcome assessment (relative to intervention) and duration.

After publishing the protocol, we also decided for the papers included in meta-analysis to record whether the immunomodulator(s) were either inhibitory or stimulatory, and whether the immunomodulatory component was a direct modulator of the target of investigation.

2.4 Reporting quality and risk of bias assessment

Two researchers (LD, IB) independently assessed reporting quality and performed a risk of bias assessment for each included paper. The SYRCLE's RoB tool(Hooijmans et al., 2014) was used to assess the risk of bias. For the bias aspect on baseline group similarity, the researchers focused on age, sex and strain. Both assessments consist of questions where the answer “yes” indicates a low risk of bias, a “no” a high risk and a “?” an unclear risk of bias. Five reporting questions were answered: (1) is it mentioned that the experiment was randomized at any stage?, (2) is it mentioned that the experiment was blinded at any stage?, (3) is a power/sample size calculation reported?, (4) is a conflict of interest statement reported?, (5) does the study mention a prespecified/preregistered protocol?. For the reporting questions, “yes” indicates reported and “no” indicates not reported. Discrepancies were resolved by discussion.

2.5 Extraction of outcome data

Next, to be able to perform the meta-analysis, aortic atherosclerotic lesion size data of each independent comparison was collected by one reviewer (LD) and checked by a second reviewer (IB). This data included the lesion size mean, SEM or SD, the unit and sample size (Supplementary Table 6). If the SEM was extracted, the SD was calculated from these data by SEM*(SQRT(n)). In order to reduce the observed heterogeneity, we decided during conduct of this systematic review to only include data containing plaque size values on the aorta, and not atherosclerosis data at other vascular locations. For aortic plaque data, the aortic root was prioritized as location over other parts of the aorta, when applicable. Furthermore, to be included in the meta-analysis, studies in which antibody treatment was applied should have included an appropriate isotype control antibody. Similarly, for lentiviral vector derived interventions a control vector should have been included in the study. Combination treatments were not included.

If the outcome data was only presented in graphs, plotdigitizer.com/app was used to extract the data for analysis. If outcome data was missing or unclear, the steps described in **Supplementary Table 3** were taken. When authors were contacted, one email and a subsequent reminder were sent. In case it was unclear whether the SD or SEM was presented, the individual data points were measured to determine whether the presented value was the SD or SEM. If the number of animals (N) was presented as a range, the individual data points were counted. If counting was not possible, the lowest value was chosen. For these and additional exceptions the detailed actions taken are presented in **Supplementary Table 3**.

2.6 Data analysis/synthesis

2.6.1 Overall effect on plaque size per target

Outcome data was grouped into the different targets: IL-1α, IL-1β, IL-6, IL-18, IL-1R, IL-6R. Treatment strategies targeting the NLRP3 inflammasome or caspase-1 were included in both the IL-1β and IL-18 groups, because both of these cytokines could have been affected by these interventions. Subsequently, for every target the data were grouped into inhibitory or stimulatory interventions. Similarly, data were grouped according to direct or indirect targeting. Additionally, we separately pooled the inhibition and stimulation data of all targets. We performed meta-analyses to determine the overall effect on plaque size for every group in Comprehensive Meta-Analysis (CMA) software version 4. The standard mean difference (Hedges g) and 95% confidence interval for plaque size between the experimental groups and control groups were calculated and subsequently pooled using the random effect model. The between study heterogeneity was estimated with I-squared (I^2). We corrected for multiple use of the control group, by adjusting the sample size of the control group by dividing by the number of times the control group was used (Duque-Quintero et al., 2022).

2.6.2 Sensitivity analyses

To assess the robustness of our results, we performed sensitivity analyses for the IL-1β and IL-18 groups, because of the inclusion of the NLRP3 inflammasome and caspase-1 data in both groups. The sensitivity analyses comprised a comparison between analyses with and without the NLRP3 inflammasome and caspase-1 data to determine whether the additional data affects the effect on plaque size.

2.6.3 Sex subgroup analyses

To determine whether sex influenced therapeutic effects on lesion size, we envisioned two scenarios in which we would be able to perform a subgroup meta-analysis for sex. One scenario would require at least three independent studies in which the effects of therapy on lesion size was presented in both sexes. Another scenario required at least 10 studies using male animals, and 10 studies using female animals. Subgroup analysis were envisioned for the second scenario. During subgroup analyses a common among-study variance component across subgroups was assumed. The subgroups (male and female) were combined using fixed effects model (Mulder et al., 2024).

2.7 Publication bias

Egger's regression to identify the risk of small study effects was conducted for all outcomes containing a minimum of 15 independent studies. Because SMDs were used in meta-analyses, the precision estimate was adjusted (Zwetsloot et al., 2017).

3. Results

3.1 Study selection

Figure 1 shows the flow chart of our study selection process. In brief; 1744 references were screened by two independent reviewers. 62 papers (Abderrazak et al., 2015; Akita et al., 2017; Bhaskar et al., 2011; Bhat et al., 2015, 2018; J. Chen et al., 2022; S. Chen et al., 2012; Christersdottir et al., 2019; de Nooijer et al., 2004; Denes et al., 2012; Dragoljevic et al., 2020; Elhage et al., 1998; Fidler et al., 2021; Freigang et al., 2011; Fukumoto et al., 1997; Fuster et al., 2017; Gomez et al., 2018; Hettwer et al., 2022; Hohensinner et al., 2021; Imai et al., 2011; Janssen et al., 2015; Jia et al., 2023; Jin et al., 2022; Karnewar et al., 2024; Ku et al., 2022; B. Li et al., 2021; X. Li et al., 2020; Y. Li et al., 2020; M. Liu et al., 2020; W. Liu et al., 2023; J. Luo et al., 2020; P. Luo et al., 2020, 2021; Ma et al., 2023; Mallat et al., 2001; Meng et al., 2016; Orecchioni et al., 2022; Schuett et al., 2012; Schwarz et al., 2023; Shentu et al., 2021; Shimokawa et al., 1996, 2001; Spartalis et al., 2021; Takeda et al., 2006; Tenger et al., 2005; Tian et al., 2020; Tissot et al., 2013; Tous et al., 2006; Traughber et al., 2023; van der Heijden et al., 2017; Vromman et al., 2019; Wan et al., 2019; Wang et al., 2020; Wen et al., 2021; Whitman et al., 2002; Wu et al., 2022; Xie et al., 2021; F. Xu et al., 2021; Z. Xu et al., 2023; Yalcinkaya et al., 2023; K. Zhang et al., 2012; Zhao et al., 2020) were included in the systematic review, of which 47 papers were included in the meta-analyses (**Figure 1**). Three comparisons from three different papers (M. Liu et al., 2020; W. Liu et al., 2023; Orecchioni et al., 2022) were not included in the systematic review, because in these mouse models gene modifications potentially interfered with the pathways we aimed to investigate.

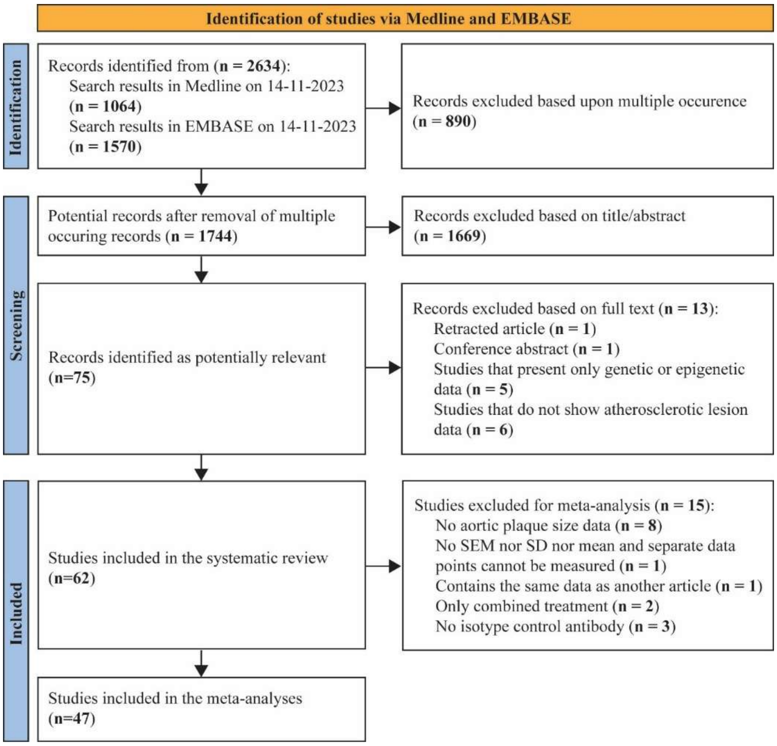


Figure 1. Flowchart of the record selection process. Illustration of the steps for the selection of relevant studies (Page, McKenzie, et al., 2021).

3.2 Study characteristics

The study characteristics of the experiments described in the 62 selected papers are displayed in **Supplementary Table 4**. The first papers were published in 1996 and 1997 (**Figure 2A**), both describing IL-1β targeting studies in pigs. Most of the included papers were published in 2020 (**Figure 2A**). In 94% of the papers, mice were used as model for atherosclerosis, in 5% of the papers pigs and in 2% rabbits (**Figure 2B**). Most of the papers (63%) used only male animals and 14% used only females for comparisons with specified sex. In two papers both males and females were used separately, while in 6% of the papers, the groups consisted of a mix of males and females. In 13%, the sex of the animals was not reported (**Figure 2C**).

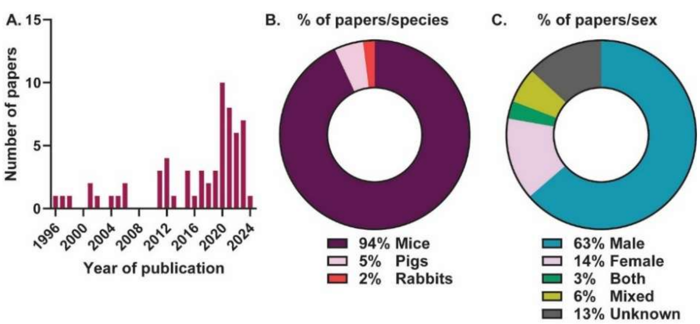


Figure 2. Publication period of the included papers and species and sex used. A. The number of papers per publication year. The percentage of papers per B. species and C. sex.

3.2.1 Characteristics of papers included in overall meta-analyses

47 papers presented all data needed regarding plaque size and were suitable to be included in the overall meta-analyses (**Figure 1**). In these papers only mice were used (**Figure 3**). For most of the papers, for which the age of the mice at outcome assessment was available, mouse age fell in the category "16 up to and including 23 weeks" (58%). Three different mouse strains were used in the papers, with the *Apoe*$^{-/-}$ mice being most abundantly applied (80% of the papers), followed by the *Ldlr*$^{-/-}$ mice (18% of the papers). Since we were interested in IL-1, IL-6 and IL-18 signaling, we defined which cytokine or cytokine receptor was targeted in the papers. In most papers (39%), IL-1β was targeted, followed by IL-18 (33%). As IL-1 and IL-18 both originate from the Interleukin-1 cytokine family, we report the outcomes of IL-18 interventions directly after IL-1 interventions. In addition, some of the papers describe more than one experiment or multiple experimental groups of interest for our analyses. We therefore extracted the individual experimental data per group, resulting in a total of 73 comparisons that were obtained from the included papers for the overall analyses.

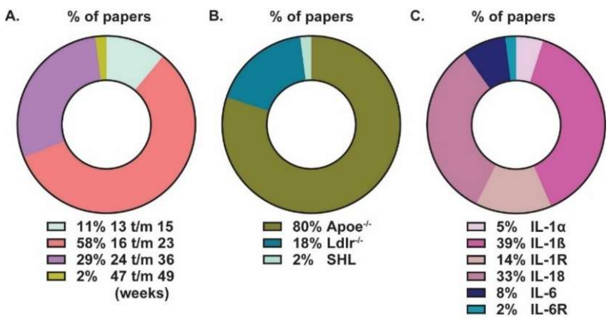


Figure 3. Study characteristics of the papers included in the meta-analyses. The percentage of papers per A. age at outcome assessment category, B. mouse strain and C. target.

3.2.2 Characteristics of papers included meta-analyses regarding sex

Sex of the animals was specified in 41 papers of the 47 included in our meta-analyses. Of these 41 papers, 80% used only male mice (n=33), 15% only female mice (n=6) and 5% used both (n=2) sexes separately in the specified comparisons (**Figure 4A**). In most of the papers, for which the age at outcome assessment was available, the age range was "16 up to and including 23 weeks" (55%) and *Apoe*$^{-/-}$ mice were mainly used (80%). Also, in this subset of papers, IL-1β (38%) was most often targeted, followed by IL-18 (33%). In **Figure 4B**, we also specified the information on study characteristics per sex.

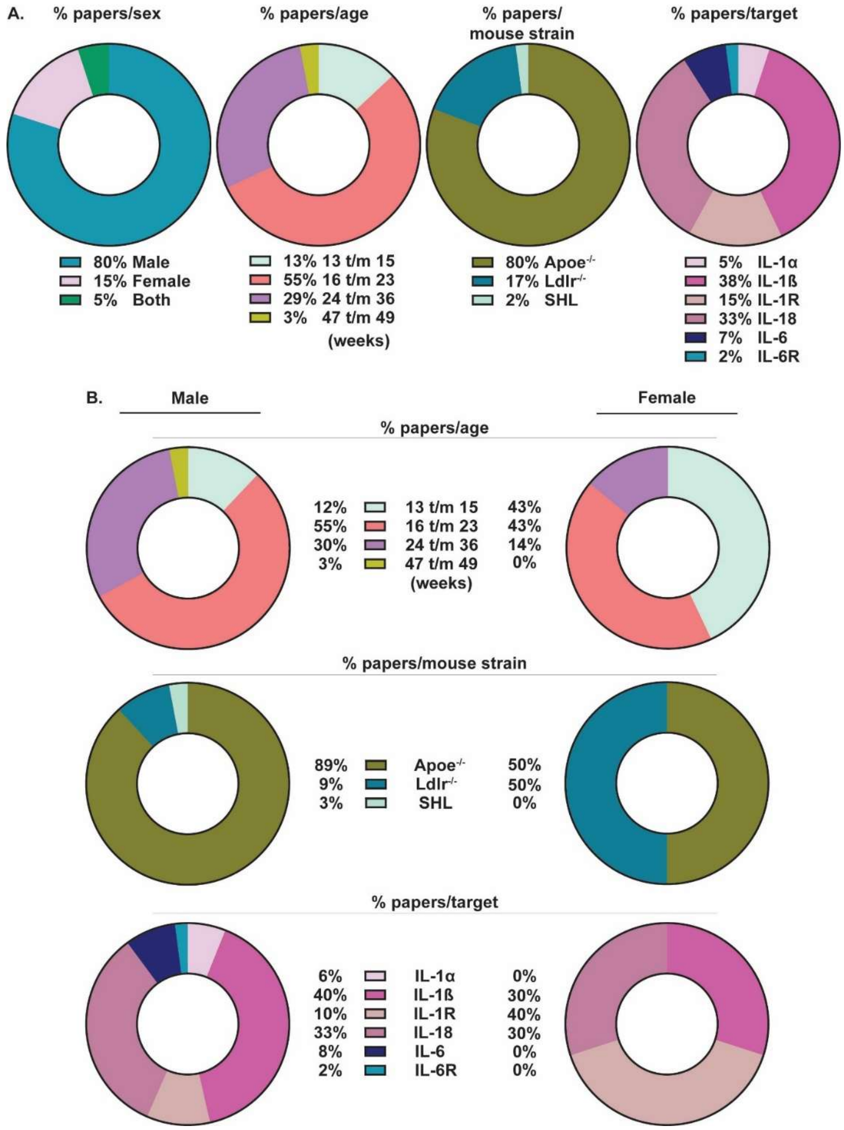


Figure 4. Study characteristics of the meta-analyses papers with specified animal sex. A. The percentage of papers per sex category, age at outcome assessment category, mouse strain and target. B. The percentage of papers for male (left) and female (right) mice per age category, mouse strain and target.

3.3 Reporting quality and risk of bias

The reporting quality (**Figure 5A**) and the risk of bias (**Figure 5B**) were assessed in all papers included in this systematic review. The detailed assessments are shown in **Supplementary Tables 5** and **6**. Regarding the reporting quality, 47% of the papers mentioned some form of randomization in the experiments, which entailed randomization of treatment groups or of treatment sites. In addition, 44% described some form of experiment blinding. Only four papers reported a power/sample size calculation. A conflict of interest statement was reported in 74%

of the papers. None of the papers mentioned a prespecified/preregistered animal study protocol (**Figure 5A**).

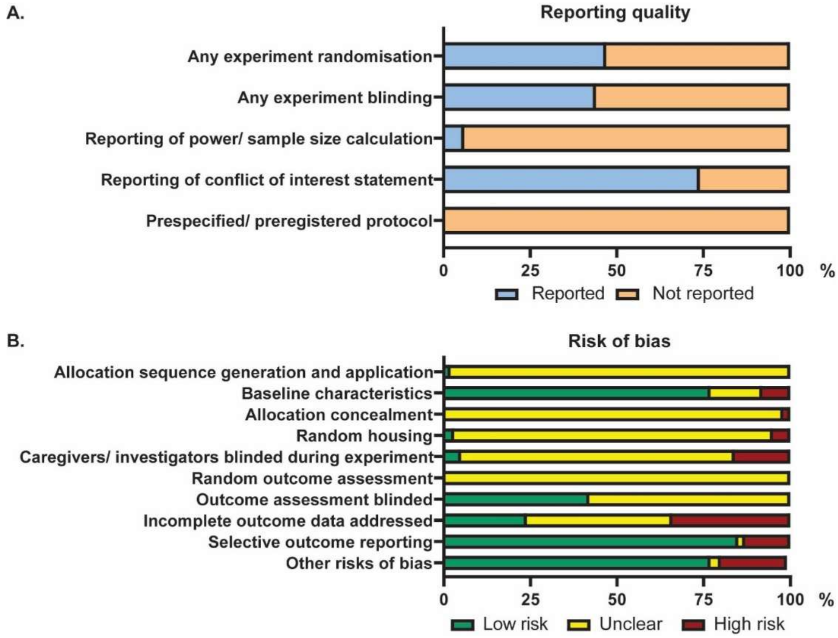


Figure 5. Risk assessments of the 62 included papers. A. Reporting quality assessment results presented as the percentage of papers that did (blue) or did not (orange) report the specific component of the total included papers. B. Risk of bias assessment results displayed as the percentage of papers in which the specific component scores a high risk (red), unclear risk (yellow) and low risk (green) as a percentage of all papers.

The risk of bias assessment showed that in only one paper a clear and adequate allocation sequence generation and application was described (**Figure 5B**). The baseline characteristics age, sex and animal strain were generally well described and did not pose a risk of bias in 77% of the papers. In only one of the papers allocation sequence concealment was specified, as in this paper group assignment was mentioned to be non-randomized and non-blinded. 92% of the papers did not mention random housing of the animals during the experiment and 79% did not mention whether the caregivers/investigators were adequately blinded during the experiment. Furthermore, it was not mentioned in any of the papers whether the outcome assessment was performed in a random fashion and 58% did not mention blinding of outcome assessment. Incomplete outcome data was adequately addressed in 24% of the papers and 85% of the papers did not selectively report outcome data. In 19% of the papers additional risks of bias were detected. For example, one paper (Bhaskar et al., 2011) compared a single concentration of a control antibody to multiple concentrations of the treatment antibody. Meng and colleagues (Meng et al., 2016) did not include an experimental method of the *in vivo* antibody treatment, only which antibodies were used, and not of the plaque staining analysis. As a last example, Xu et al. (Z. Xu et al., 2023) described an n-value of 3, which is very limited for atherosclerosis experiments (Daugherty et al., 2017).

3.4 Meta-analyses

The extracted outcome data is presented in **Supplementary Table 7**. Meta-analyses results are presented in **Table 1** per cytokine modulation group. Direct inhibition of IL-1α led to a significantly smaller plaque size. No data was available regarding indirect inhibition, nor direct and indirect stimulation of IL-1α. Direct and indirect inhibition of IL-1β significantly decreased plaque size and direct stimulation seems to increase plaque size, although this dataset contained only one study. Indirect stimulation of IL-1β did not significantly affect plaque size. Plaque size significantly decreased after direct and indirect inhibition of the IL-1R. No data regarding stimulation of the IL-1R was available. IL-18 inhibition (both direct and indirect) significantly decreased plaque size and direct and indirect stimulation of IL-18 significantly increased plaque size. Finally, direct and indirect inhibition of IL-6 resulted in significantly smaller plaques. Remarkably, direct stimulation of IL-6 also significantly decreased plaque size, but again here, this dataset contained only one comparison. There was no data on indirect IL-6 stimulation. Regarding the IL-6R, there was only one comparison investigating the effect of direct inhibition, but this did not induce a significant effect on plaque size. No data regarding indirect inhibition of Il-6R or IL-6R stimulation was available. The overall meta-analysis for all comparisons investigating the effect of inhibition showed that plaque size significantly decreased upon inhibition as indicated by a negative standardized mean difference (-1.5 [-1.8 to -1.2]), where a value of 0 would indicate no difference in effect. All comparisons investigating the effect of stimulation, showed an increase in lesion size increased after stimulation of the pathways (1.2 [0.3 to 2.1]) (**Table 1**). Together, these data illustrate a pro-atherogenic effect of these cytokines, with therapeutic efficacy upon inhibiting these cytokine pathways.

Table 1. Overall direction of effect on plaque size upon modulation of IL-1, IL-18, IL-6 or their receptors. Meta-analyses results for every target group, including the data of inhibition of all targets (inhibition total) or the data of stimulation of all targets (stimulation total). Number (N) of studies, N of comparisons, overall effect on plaque size (standardized mean difference (SMD) ± 95% confidence interval ($CI_{95\%}$)) and I^2 are presented per group.

Cytokine signaling target	N studies	N comparisons	Overall effect(SMD ± $CI_{95\%}$)	I^2
IL-1α inhibition direct	3	4	-1.4 [-2.4 to -0.4]	80
IL-1α inhibition indirect	0	0	-	-
IL-1α stimulation direct	0	0	-	-
IL-1α stimulation indirect	0	0	-	-
IL-1β inhibition direct	7	12	-0.5 [-0.9 to -0.1]	51
IL-1β inhibition indirect	16	24	-2.2 [-2.7 to -1.6]	77
IL-1β stimulation direct	1	1	5.0 [2.8 to 7.3]	0
IL-1β stimulation indirect	2	3	2.0 [-0.1 to 4.1]	91
IL-1R inhibition direct	8	13	-1.0 [-1.6 to -0.5]	71
IL-1R inhibition indirect	1	1	-1.4 [-2.5 to -0.2]	0
IL-1R stimulation direct	0	0	-	-
IL-1R stimulation indirect	0	0	-	-
IL-18 inhibition direct	1	1	-0.8 [-1.5 to -0.1]	0
IL-18 inhibition indirect	16	24	-2.2 [-2.7 to -1.6]	77
IL-18 stimulation direct	4	6	0.9 [0.2 to 1.6]	68
IL-18 stimulation indirect	1	2	0.7 [0.0 to 1.4]	27
IL-6 inhibition direct	1	3	-2.0 [-3.2 to -0.7]	68
IL-6 inhibition indirect	3	3	-4.5 [-6.4 to -2.7]	52
IL-6 stimulation direct	1	1	-2.5 [-4.0 to -1.0]	0
IL-6 stimulation indirect	0	0	-	-
IL-6R inhibition direct	1	1	0.4 [-0.4 to 1.1]	0
IL-6R inhibition indirect	0	0	-	-
IL-6R stimulation direct	0	0	-	-
IL-6R stimulation indirect	0	0	-	-
Inhibition total	39	62	-1.5 [-1.8 to -1.2]	78
Stimulation total	8	11	1.2 [0.3 to 2.1]	86

3.4.1 Sensitivity analyses

Treatments targeting the NLRP3 inflammasome or caspase-1 can affect both the IL-1β and IL-18 pathway and were therefore included in both these treatment groups. To determine whether the NLRP3 inflammasome and caspase-1 data affects the effect estimate of the IL-1β and IL-18 groups, sensitivity analyses were performed excluding the NLRP3 inflammasome and caspase-1 comparisons (**Table 2**). In general, our analyses seem robust and nearly all effects remain the same, suggesting that efficacy of such interventions provide similar outcomes as direct IL-1β and IL-18 interventions. The only difference was the effect of IL-1β indirect stimulation. However, it has to be taken into account that the sensitivity analysis of IL-1β indirect stimulation was based on one single study.

Table 2. Sensitivity analysis for IL-1β and IL-18. The NLRP3 inflammasome and caspase-1 comparisons described in the right part of the table are included in the meta-analyses, but not in the sensitivity analyses of the IL-1β and IL-18 groups. Number (N) of studies (stu), N of comparisons (com), overall effect on plaque size (standardized mean difference (SMD) ± 95% confidence interval ($CI_{95\%}$)) and I^2 are presented for the analyses.

Meta-analysis					**Sensitivity analysis**				**NLRP3 inflammasome and caspase-1 comparisons included in IL-1β and IL-18 meta-analyses**		
Cytokine signaling target	**N stu**	**N com**	**Overall effect (SMD ± $CI_{95\%}$)**	**I^2**	**N stu**	**N com**	**Overall effect (SMD ± $CI_{95\%}$)**	**I^2**	**Cytokine signaling target**	**N stu**	**N com**
IL-1β inhibition direct	7	12	-0,5 [-0,9 to -0,1]	51	7	12	-0,5 [-0,9 to -0,1]	51	NLRP3 inflammasome inhibition direct	0	0
IL-1β inhibition indirect	16	24	-2,2 [-2,7 to -1,6]	77	0	0	-	-	NLRP3 inflammasome inhibition indirect	14	19
IL-1β stimulation direct	1	1	5,0 [2,8 to 7,3]	0	1	1	5,0 [2,8 to 7,3]	0	NLRP3 inflammasome stimulation direct	0	0
IL-1β stimulation indirect	2	3	2,0 [-0,1 to 4,1]	91	1	1	5,3 [3,3 to 7,2]	0	NLRP3 inflammasome stimulation indirect	1	2
IL-18 inhibition direct	1	1	-0,8 [-1,5 to -0,1]	0	1	1	-0,8 [-1,5 to -0,1]	0	Caspase-1 inhibition direct	0	0
IL-18 inhibition indirect	16	24	-2,2 [-2,7 to -1,6]	77	0	0	-	-	Caspase-1inhibition indirect	2	5
IL-18 stimulation direct	4	6	0,9 [0,2 to 1,6]	68	4	6	0,9 [0,2 to 1,6]	68	Caspase-1 stimulation direct	0	0
IL-18 stimulation indirect	1	2	0,7 [0,0 to 1,4]	27	0	0	-	-	Caspase-1 stimulation indirect	0	0

3.4.2 The effect of sex

To determine the effect of the sex on lesion size we envisioned two scenarios (see methods). Regarding scenario 1; only two studies investigated the difference between the sexes. As a consequence, no formal meta-analysis is conducted. The first study, by Elhage et al. described a significant difference between males and females in the combined effect of multiple treatments on the lesion size, including an IL-1 receptor antagonist (IL-1ra). For IL-1ra a significantly smaller lesion size was described for both males and females. However, the authors did not formally assess the difference between sexes for this specific treatment separately (Elhage et al., 1998). The second study, by Traughber et al., mentioned that the lesion size was ~50% smaller upon treatment in both male and female mice, but no formal assessment of the difference between males and females was provided (Traughber et al., 2023). The forest plot with these two studies is shown in **Figure 6**.

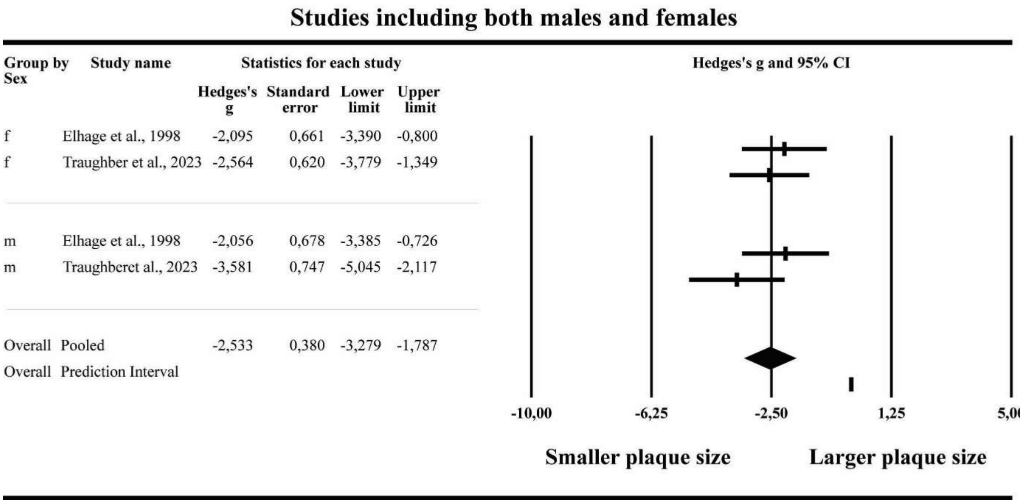


Figure 6. Forrest plot for plaque size of studies that investigated both males and females. The numbers are the Hedges's g, standard error and the lower and upper limit of the 95% confidence interval (= $CI_{95\%}$). The diamond indicates the overall pooled effect (Elhage et al., 1998; Traughber et al., 2023).

The second scenario we envisioned were subgroup analyses regarding sex. The two studies investigating both males and females separately (Elhage et al., 1998; Traughber et al., 2023) were included in the subgroup analysis. Only the three groups "IL-1β inhibition indirect", "IL-18 inhibition indirect" and "inhibition total" had male subgroups that were large enough for formal subgroup analyses (**Supplementary Table 8)**. For males the plaque size was significantly smaller upon inhibitory treatment, indicated by the negative SMD ± $CI_{95\%}$, which was similar to the overall effect (**Table 3**). The number of studies investigating IL-6/IL-6R interventions was too low for subgroup analyses.

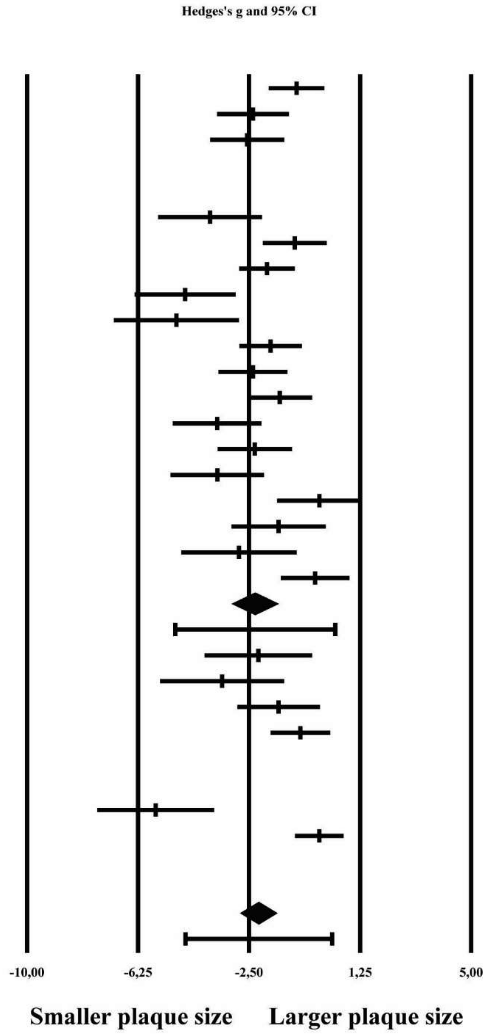
Table 3. Male subgroup analyses for plaque size upon cytokine signaling inhibition. Number (N) of studies and comparisons, overall effect on plaque size (standardized mean difference (SMD) ±95% confidence interval ($CI_{95\%}$)) per sex, I^2 are presented.

Cytokines signaling target	Sex	N studies	N comparisons	Effect (SMD ± $CI_{95\%}$)	I^2
IL-1β/IL-18 inhibition indirect	Overall	16	22	-2,2 [-2,7 to -1,6]	77
	Females	2	3	Not calculated	
	Males	12	15	-2,3 [-3,0 to -1,6]	74
Inhibition total	Overall	39	62	-1,5 [-1,8 to -1,2]	78
	Females	7	10	Not calculated	
	Males	28	42	-1,6 [-1,9 to -1,2]	79

In the forest plots in Figure 7, the Hedge's g values and confidence intervals are displayed, which show that the inhibitory intervention studies generally show reduced lesion size upon treatment, indicated by the negative Hedge's g values (those below 0). Although the number of studies in the subgroup of females was too low to reliably interpret the subgroup effect, visual inspection of the forest plots suggested no difference in effect size between females and males, as the confidence intervals of the studies conducted in females completely overlap with the studies conducted in males (**Figure 7A** and **B**).

A. **IL-1ß inhibition indirect**

Group by Sex	Study name	Hedges's g	Standard error	Lower limit	Upper limit
		Statistics for each study			
f	Fuster et al., 2017	-0,894	0,462	-1,800	0,012
f	Fuster et al., 2017	-2,369	0,600	-3,545	-1,193
f	Traughber et al., 2023	-2,564	0,620	-3,779	-1,349
m	Zhao et al., 2020	-3,819	0,878	-5,540	-2,098
m	B. Li et al., 2021	-0,955	0,532	-1,997	0,088
m	Hohensinner et al., 2021	-1,895	0,462	-2,800	-0,989
m	X. Li et al., 2020	-4,660	0,852	-6,330	-2,990
m	J. Luo et al., 2020	-4,954	1,062	-7,034	-2,873
m	Ma et al., 2023	-1,772	0,522	-2,795	-0,749
m	Ma et al., 2023	-2,371	0,576	-3,499	-1,243
m	Tian et al., 2020	-1,462	0,539	-2,518	-0,406
m	Traughber et al., 2023	-3,581	0,747	-5,045	-2,117
m	Wang et al., 2020	-2,304	0,624	-3,527	-1,081
m	Wen et al., 2021	-3,574	0,789	-5,120	-2,027
m	Zhao et al., 2020	-0,124	0,713	-1,522	1,274
m	Zhao et al., 2020	-1,504	0,796	-3,065	0,056
m	Zhao et al., 2020	-2,842	0,978	-4,759	-0,925
m	Y. Li et al., 2020	-0,268	0,574	-1,394	0,858
m	Pooled	-2,290	0,371	-3,016	-1,563
m	Prediction Interval	-2,290		-4,989	0,410
mix	Jin et al., 2022	-2,186	0,908	-3,967	-0,406
mix	Jin et al., 2022	-3,411	1,051	-5,471	-1,350
mix	Jin et al., 2022	-1,503	0,694	-2,862	-0,143
mix	Jin et al., 2022	-0,764	0,495	-1,735	0,206
unknown	Wan et al., 2019	-5,654	0,991	-7,597	-3,711
unknown	Schwarz et al., 2023	-0,128	0,403	-0,917	0,662
Overall	Pooled	-2,171	0,292	-2,744	-1,598
Overall	Prediction Interval	-2,171		-4,644	0,303



B.

Inhibition total

Group by Sex	Study name	Hedges's g	Standard error	Lower limit	Upper limit
f	Christersdottir et al., 2019	-1,351	0,562	-2,452	-0,250
f	Dragoljevic et al., 2020	-0,713	0,504	-1,701	0,275
f	Elhage et al., 1998	-2,095	0,661	-3,390	-0,800
f	Fidler et al., 2021	-0,179	0,474	-1,108	0,750
f	Fidler et al., 2021	-0,181	0,478	-1,117	0,755
f	Fidler et al., 2021	0,170	0,282	-0,382	0,722
f	Fuster et al., 2017	-0,894	0,462	-1,800	0,012
f	Fuster et al., 2017	-2,369	0,600	-3,545	-1,193
f	Traughber et al., 2023	-2,564	0,620	-3,779	-1,349
f	Yalcinkaya et al., 2023	-0,470	0,361	-1,178	0,238
m	Bhaskar et al., 2011	-1,573	0,686	-2,917	-0,229
m	Bhaskar et al., 2011	-0,906	0,638	-2,155	0,344
m	Bhaskar et al., 2011	-1,207	0,679	-2,538	0,124
m	Chen et al., 2012	-2,324	0,564	-3,430	-1,218
m	Denes et al., 2012	-0,595	0,405	-1,388	0,199
m	Denes et al., 2012	-0,565	0,498	-1,541	0,411
m	Elhage et al., 1998	-2,056	0,678	-3,385	-0,726
m	Gomez et al., 2018	0,086	0,533	-0,960	1,131
m	Hohensinner et al., 2021	-1,895	0,462	-2,800	-0,989
m	Karnewar et al., 2024	2,328	0,773	0,813	3,842
m	Ku et al., 2022	0,211	0,614	-0,992	1,414
m	Ku et al., 2022	-1,771	0,704	-3,150	-0,391
m	Ku et al., 2022	-1,103	0,649	-2,376	0,170
m	B. Li et al., 2021	-0,955	0,532	-1,997	0,088
m	X. Li et al., 2020	-4,660	0,852	-6,330	-2,990
m	Y. Li et al., 2020	-0,268	0,574	-1,394	0,858
m	M. Liu et al., 2020	-0,836	0,448	-1,715	0,042
m	W. Liu et al., 2023	0,358	0,364	-0,355	1,072
m	J. Luo et al., 2020	-4,954	1,062	-7,034	-2,873
m	P. Luo et al., 2020	-4,567	1,297	-7,109	-2,025
m	P. Luo et al., 2021	-6,634	1,455	-9,486	-3,782
m	Ma et al., 2023	-1,772	0,522	-2,795	-0,749
m	Ma et al., 2023	-2,371	0,576	-3,499	-1,243
m	Mallat et al., 2001	-0,803	0,358	-1,504	-0,103
m	Meng et al., 2016	-2,677	0,633	-3,918	-1,436
m	Schuett et al., 2012	-0,916	0,572	-2,037	0,205
m	Schuett et al., 2012	-3,310	0,782	-4,842	-1,778
m	Schuett et al., 2012	-1,912	0,553	-2,995	-0,828
m	Tian et al., 2020	-1,462	0,539	-2,518	-0,406
m	Tissot et al., 2013	-1,768	0,471	-2,691	-0,845
m	Traughber et al., 2023	-3,581	0,747	-5,045	-2,117
m	Vromman et al., 2019	-1,269	0,492	-2,232	-0,305
m	Vromman et al., 2019	-0,023	0,449	-0,903	0,857
m	Vromman et al., 2019	-0,230	0,419	-1,052	0,592
m	Vromman et al., 2019	-0,724	0,431	-1,569	0,121
m	Wang et al., 2020	-2,304	0,624	-3,527	-1,081
m	Wen et al., 2021	-3,574	0,789	-5,120	-2,027
m	Xu et al., 2023	-4,067	1,343	-6,700	-1,434
m	Zhao et al., 2020	-3,819	0,878	-5,540	-2,098
m	Zhao et al., 2020	-0,124	0,713	-1,522	1,274
m	Zhao et al., 2020	-1,504	0,796	-3,065	0,056
m	Zhao et al., 2020	-2,842	0,978	-4,759	-0,925
m	Pooled	-1,559	0,193	-1,938	-1,180
m	Prediction Interval	-1,559		-3,726	0,609
mix	Hettwer et al., 2022	-0,836	0,414	-1,646	-0,025
mix	Hettwer et al., 2022	-0,973	0,427	-1,810	-0,136
mix	Jin et al., 2022	-2,186	0,908	-3,967	-0,406
mix	Jin et al., 2022	-3,411	1,051	-5,471	-1,350
mix	Jin et al., 2022	-1,503	0,694	-2,862	-0,143
mix	Jin et al., 2022	-0,764	0,495	-1,735	0,206
unknown	Schwarz et al., 2023	-0,128	0,403	-0,917	0,662
unknown	Takeda et al., 2006	-3,352	0,758	-4,838	-1,866
unknown	Wan et al., 2019	-5,654	0,991	-7,597	-3,711
unknown	Wu et al., 2022	-1,372	0,583	-2,514	-0,229
Overall	Pooled	-1,491	0,158	-1,800	-1,182
Overall	Prediction Interval	-1,491		-3,610	0,627

Hedges's g and 95% CI

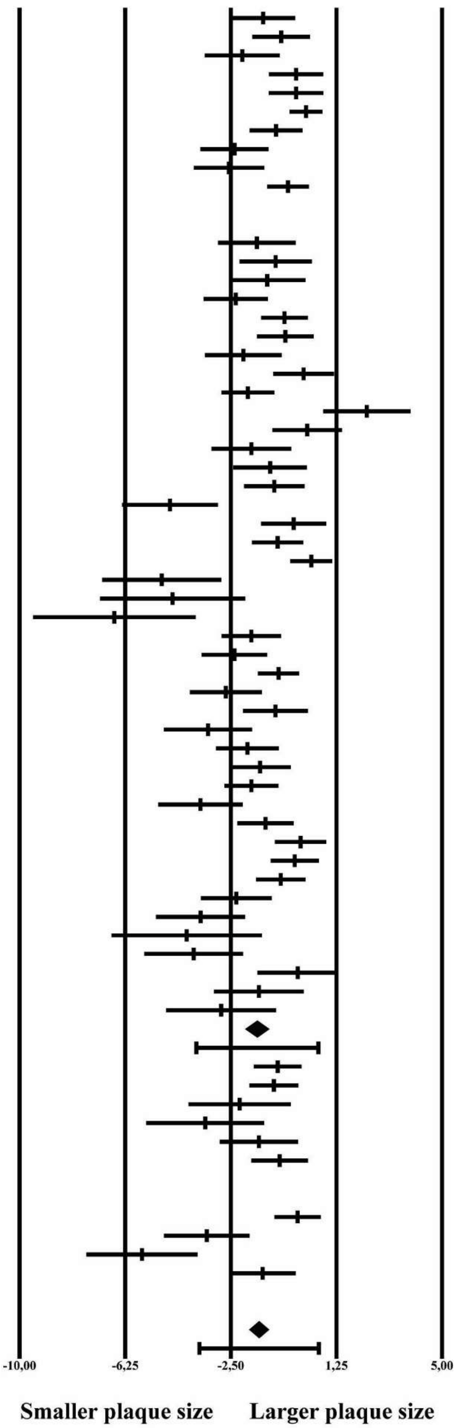


Figure 7. Forrest plot for plaque size for the groups with enough studies for a male subgroup analysis. A. For the IL-1β or IL-18 signaling inhibition group. B. For the total cytokine signaling inhibition group. The numbers are the Hedges's g, standard error and the lower and upper limit of the 95% confidence interval (= $CI_{95\%}$). The diamonds indicate the pooled effect of the male subgroup and overall.

3.5 PB analysis

The risk of potential publication bias could only be assessed for indirect inhibition of IL-1β (n=16) and IL-18 (n=16) and for inhibition total (n=39). There was no evidence for publication bias according to Egger's regression test (indirect inhibition of IL-1β: p=0.57, indirect inhibition of IL-18: p=0.57 and total inhibition: p=0.64).

4. Discussion

In this systematic review, we aimed to assess experimental animal sex in atherosclerosis studies with (anti-)inflammatory therapeutics and determine whether the sex of the animal is an important variable to be included in such *in vivo* atherosclerosis studies. To do so, we specifically focused on literature investigating the modulation of IL-1, IL-18 and IL-6 cytokine signaling in atherosclerotic animal models with atherosclerotic plaque size as main read-out. These inflammatory pathways were selected as they are of interest for clinical development to reduce the inflammatory cardiovascular risk upon lipid-lowering therapy. We here show, by including papers up to the end of 2023, that inhibition of these cytokine signaling pathways collectively reduced aortic plaque development in atherosclerotic mice. Subgroup analyses for the combined inhibition data showed a similar result in male mice. For female mice, no formal analyses could be conducted due to limited number of studies, however, visual inspection of the forest plot suggests no significant differences in effect between males and females.

In this systematic review, atherosclerotic plaque size was initially analyzed per cytokine or receptor, and in a second phase, the inhibitory interventions, and respectively the stimulating strategies were combined. In general, we show that inhibition of the pro-inflammatory cytokines significantly decreased plaque size, and stimulation significantly increased plaque size. An exception was a study with direct stimulation of IL-6, which led to a significantly smaller plaque size. This outcome could be explained by the controversial role of IL-6 in atherosclerosis (Reiss et al., 2017).

Our results confirm the importance of IL-1, IL-18 and IL-6 signaling in atherosclerosis and support the development of such anti-inflammatory therapies for human application. Strengthening this conclusion is the relevance of these studies to human disease, as in the CANTOS trial the recurrence of cardiovascular events was reduced upon anti-IL-1β treatment (P. M. Ridker et al., 2017), and in the RESCUE trial treatment of high cardiovascular risk patients with an anti- IL-6 antibody lowered, hsCRP (P. Ridker et al., 2021). Although plaque measurements were not an endpoint in these clinical trials, plaque burden is shown to be a predictor of cardiovascular events in patients (Erlinge et al., 2021; McPherson et al., 2012; Stone et al., 2011; Vergallo et al., 2025). Therefore, the outcome parameter in this systematic review, plaque size, is an important aspect in the translation to human disease, but it is important to note that plaque composition aids in defining whether a plaque is high-risk. In future systematic review studies on inflammatory therapies in animal models of atherosclerosis, plaque composition would be a useful addition to the outcome parameters.

The aim of this study was to explore potential sex differences in therapeutic efficacy of targeting IL-1, IL-18 and IL-6 cytokine pathways in preclinical atherosclerosis models, which would provide knowledge on which sex to include in such studies or whether animal sex can be excluded as a variable. Surprisingly, studies using female mice were very limited as evident from our analysis, and mainly male mice were used for the included studies, at least in papers up to the end of 2023. The observations from our subgroup analyses show that therapeutic efficacy is highly significant in male mice, rendering the male mouse a valid model for such studies. From the limited number of studies with female mice, therapeutic efficacy seemed similar as compared to male mice, however due to the lack of power we cannot formally conclude this. In general, animal atherosclerosis studies are mostly performed in either male or female animals. Studies conducted in both sexes rarely contain a statistical test to determine whether sex is an independent variable (Man et al., 2020). To enable formal tests on sex differences, we recommend scientists to include both males and females in their studies, and assess the difference between the sexes. In our review, we only found two studies that used both male and females separately (Elhage et al., 1998; Traughber et al., 2023), but neither formally assessed the difference in effect on lesion size between males and females for our treatment of interest. Previously, male mice were shown to have more inflamed, but smaller lesions compared to females (Man et al., 2020). These differences strengthen our recommendation to use both sexes in mice studies to enable the establishment of sex effects in anti-inflammatory studies, in line with the ARRIVE guidelines as well as the recommendations from the American Heart Association (Daugherty et al., 2017). These differences in inflammation, also shows the importance of inclusion of additional plaque components as outcome parameters in future systematic reviews.

This is the first systematic review in the field investigating animal sex in studies assessing the efficacy of preclinical anti-inflammatory treatments. Our main conclusions are based on studies in which 55% of the mice were 16-23 weeks old and 29% 24-36 weeks. Mice are defined mature adult in the age range from 3-6 months, middle aged from 10-15 months, old from 18-24 months and very old over 24 months. Thus, our conclusions are based on relatively young mice. Man et al. summarized that in general, female *Apoe*$^{-/-}$ and *Ldlr*$^{-/-}$ mice have larger plaques compared to male mice this comprises for *Apoe*$^{-/-}$ in the aortic root through 6 months age, in the whole aorta of 4 to 12 months old on a normal chow diet, and for *Ldlr*$^{-/-}$ in the aortic root and whole aorta through 6 months of age (Man et al., 2020). However, there are some exceptions (Man et al., 2020). A number of studies show a similar plaque size for 1 to 15 months male and female

Apoe$^{-/-}$ mice on a normal chow diet in the whole aorta (Champagne et al., 2009; Jeon et al., 2010; M. Liu et al., 2016; Maier et al., 2017; Marek et al., 2017; Matsumoto et al., 2016) and some studies show that 3 to 8 months male *Apoe*$^{-/-}$ mice have larger lesions in the whole aorta than females on a normal chow diet (M. Liu et al., 2016; G. Zhang et al., 2018). *Apoe*$^{-/-}$ mice, up to 22 weeks of age and on an atherogenic diet have similar plaques in male and female whole aortas. However, in some studies with a long duration of an atherogenic diet male *Apoe*$^{-/-}$ mice of 6 or 12 months old had larger lesions than females (Chiba et al., 2011; Tangirala et al., 1995). For studies using *Ldlr*$^{-/-}$ mice, there are some exceptions as well. One study using 6 months old male mice showed larger lesions in the descending aorta compared to female mice after 5 months of an atherogenic diet(Parks et al., 2006). In a similar study, one-year-old males had larger lesions compared to females in the whole aorta after 6 months of an atherogenic diet (Tangirala et al., 1995). Smit et al. showed that the lesion size in the aortic root of 22 months old *Ldlr*$^{-/-}$ mice was similar in males and females (Smit et al., 2024). Overall, the age of the mice should be taken into account when considering the exclusion of sex as a variable.

To account for the inclusion of NLRP3 inflammasome and caspase-1 targeting in both IL-1β and IL-18 groups for meta-analyses, we performed sensitivity analyses. These indicated that our results were robust and our overall conclusions were not affected. In addition, analyses of between-study heterogeneity revealed moderate to severe levels. Heterogeneity is expected in animal research due to the often-exploratory approach, meaning some of it is intentionally induced. To address this, we applied a random effects model, and examined potential causes of heterogeneity through subgroup analyses regarding sex. Unfortunately, the number of studies using females was too low to formally assess. Furthermore, in this systematic review only studies using mice were identified. Whether the effects are similar in other species remains unclear, however the number of atherosclerosis studies in other animal models is very limited. Overall, most of the animal studies that we included failed to report a number of important study details, hampering risk of bias analyses. While this is common in the field, the lack of reporting on important methodological details suggests a certain degree of neglect of methods designed to reduce bias, potentially leading to skewed results and severely hindering the ability to draw reliable conclusions from the included animal studies.

5. Conclusion

All together, we show that inhibition of the cytokine signaling pathways of IL-1, IL-6 and IL-18 collectively reduced aortic plaque development in atherosclerotic mice, which was predominantly studied in male mice. Our analyses into sex differences suggest no difference between males and females, although we could not formally test this due to the limited number of studies in the female subgroup. More studies using female animals in this research area are thus needed.

6. Author contributions

Lucie Delfos: conceptualization, investigation, methodology, formal analysis, visualization, writing – original draft, writing – review and editing. **Cody Huis:** conceptualization, investigation, methodology, writing – review and editing. **Nadia Imani:** investigation, writing – review and editing. **Jeanine E. Roeters van Lennep:** conceptualization. **Carlijn R. Hooijmans:** conceptualization, investigation, methodology, formal analysis, resources, writing – review and editing. **Ilze Bot:** conceptualization, investigation, methodology, supervision, writing – review and editing, funding acquisition.

7. Declaration of competing interest

The authors declare no competing interests.

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Supplementary Tables

Supplementary Table 1. Search string MEDLINE.

Supplementary Table 1. Medline (PubMed) search strings			
String	**String name**	**Terms**	**HITS (14-11-2023)**
1	Atherosclerosis	exp Atherosclerosis/ or "Atherosclerosis".ti,ab,kf. or "Atheroscleroses".ti,ab,kf. or "Atherogenesis".ti,ab,kf. or Plaque, Atherosclerotic/ or "Plaque Atherosclerotic".ti,ab,kf. or "Plaques Atherosclerotic".ti,ab,kf. or "Atherosclerotic Plaques".ti,ab,kf. or "Atherosclerotic Plaque".ti,ab,kf. or "Fatty Streak Arterial".ti,ab,kf. or "Arterial Fatty Streaks".ti,ab,kf. or "Fibroatheroma".ti,ab,kf. or "Fibroatheromas".ti,ab,kf. or "Fibroatheromatous".ti,ab,kf. or "Atheroma".ti,ab,kf. or "Atheromas".ti,ab,kf. or "Atheromatous".ti,ab,kf.	183425
2	Cytokine and Receptor tiab	("Interleukin-6" or "Interleukin 6" or "IL6" or "IL-6" or "IL 6" or "B-Cell Stimulatory Factor 2" or "B-Cell Stimulatory Factor-2" or "B-Cell Differentiation Factor-2" or "B Cell Differentiation Factor 2" or "BSF-2" or "Hybridoma Growth Factor" or "IFN-beta 2" or "Plasmacytoma Growth Factor" or "Hepatocyte-Stimulating Factor" or "Hepatocyte Stimulating Factor" or "MGI-2" or "Myeloid Differentiation-Inducing Protein" or "Myeloid Differentiation Inducing Protein" or "B-Cell Differentiation Factor" or "B Cell Differentiation Factor" or "Differentiation Factor B-Cell" or "Differentiation Factor B Cell" or "IL-6" or "Interferon beta-2" or "Interferon beta 2" or "beta-2 Interferon" or "B Cell Stimulatory Factor-2" or "B Cell Stimulatory Factor 2" or "Receptor CD126" or "CD126 Antigens" or "Interleukin-1" or "Interleukin 1" or "Interleukin1" or "IL-1" or "IL 1" or "IL1" or "IL1a" or "IL-1a" or "T Helper Factor" or "Lymphocyte-Activating Factor" or "Lymphocyte Activating Factor" or "Epidermal Cell Derived Thymocyte-Activating Factor" or "Epidermal Cell Derived Thymocyte Activating Factor" or "Interleukin I" or "IL-I alpha" or "IL-I beta" or "IL-1alpha" or "Interleukin 1alpha" or "Hematopoietin-1" or "Hematopoietin 1" or "IL-1beta" or "IL-1b" or "IL1b" or "Interleukin 1beta" or "Catabolin" or "Interleukin-18" or "Interleukin 18" or "Interleukin18" or "IFN-gamma-Inducing Factor" or "IL-18" or "Interferon-gamma-Inducing Factor" or "IL18" or "IL 18").ti,ab,kf.	292907

3	Modulation tiab	("Anti-Inflammatories" or "Antiinflammatories" or "Antiinflammatory Agent" or "Antiinflammatory Agents" or "Anti-Inflammatory Agent" or "Immunological Factors" or "Immune Factors" or "Immune Factor" or "Immunological Factor" or "Biomodulators" or "Biomodulator" or "Pro" or "Pro-" or "Procytokine" or "Procytokines" or "Prointerleukin" or "ProIL" or "Proreceptor" or "Pro-cytokine" or "Pro-cytokines" or "Pro-interleukin" or "Pro-IL" or "Pro-receptor" or "Anti" or "Anti-" or "Anticytokine" or "Anticytokines" or "Antiinterleukin" or "AntiIL" or "Antireceptor" or "Anti-cytokine" or "Anti-cytokines" or "Anti-interleukin" or "Anti-IL" or "Anti-receptor" or "Antibody" or "Antibodies" or "Therapeutic" or "Therapeutics" or "Therapy" or "Therapies" or "Small molecule" or "Small molecules" or "Small-molecule" or "Small-molecules" or "Agonist" or "Agonists" or "Antagonist" or "Antagonists" or "Modulate" or "Modulates" or "Modulated" or "Modulator" or "Modulators" or "Modulating" or "Modulation" or "Inhibit" or "Inhibits" or "Inhibited" or "Inhibition" or "Inhibitor" or "Inhibiting" or "Inhibitors" or "Inhibitory" or "Stimulate" or "stimulates" or "stimulated" or "Stimulation" or "Stimulator" or "Stimulators" or "Stimulatory" or "Stimulating" or "Treatment" or "Treat" or "Treats" or "Treated" or "Treating" or "Immunomodulation" or "Immunomodulating" or "Immunomodulator" or "Immunomodulators" or "Immunomodulate" or "Immunomodulates" or "Immunomodulated" or "Immunomodulatory" or "Immunomodulant" or "Immunomodulants" or "Immunemodulation" or "Immunemodulating" or "Immunemodulator" or "Immunemodulators" or "Immunemodulate" or "Immunemodulates" or "Immunemodulated" or "Immunemodulatory" or "Immunemodulant" or "Immunemodulants" or "Immuno-modulation" or "Immuno-modulating" or "Immuno-modulator" or "Immuno-modulators" or "Immuno-modulate" or "Immuno-modulates" or "Immuno-modulated" or "Immuno-modulatory" or "Immuno-modulant" or "Immuno-modulants" or "Immune-modulation" or "Immune-modulating" or "Immune-modulator" or "Immune-modulators" or "Immune-modulate" or "Immune-modulates" or "Immune-modulated" or "Immune-modulatory" or "Immune-modulant" or "Immune-modulants" or "IMiDs" or "Modulant" or "Modulants" or "Immuneregulation" or "Immuneregulating" or "Immuneregulator" or "Immuneregulators" or "Immuneregulatory" or "Immuneregulate" or "Immuneregulates" or "Immuneregulated" or "Immunoregulation" or "Immunoregulating" or "Immunoregulator" or "Immunoregulators" or "Immunoregulatory" or "Immunoregulate" or "Immunoregulates" or "Immunoregulated" or "Immune-regulation" or "Immune-regulating" or "Immune-regulator" or "Immune-regulators" or "Immune-regulatory" or "Immune-regulate" or "Immune-regulates" or "Immune-regulated" or "Immuno-regulation" or "Immuno-regulating" or "Immuno-regulator" or "Immuno-regulators" or "Immuno-regulatory" or "Immuno-regulate" or "Immuno-regulates" or "Immuno-regulated" or "Immunestimulation" or "Immunestimulating" or "Immunestimulator" or "Immunestimulators" or "Immunestimulatory" or "Immunestimulate" or "Immunestimulates" or "Immunestimulated" or "immunestimulant" or "immunestimulants" or "Immunostimulation" or "Immunostimulating" or "Immunostimulator" or "Immunostimulators" or "Immunostimulatory" or "Immunostimulate" or "Immunostimulates" or "Immunostimulated" or "immunostimulant" or "immunostimulants" or "Immune-stimulation" or "Immune-stimulating" or "Immune-stimulator" or "Immune-stimulators" or "Immune-stimulatory" or "Immune-stimulate" or "Immune-	21525375

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		"retainer" or "retainers" or "retaining" or "retain" or "retains" or "retained" or "retention" or "limiter" or "limiters" or "limiting" or "limit" or "limits" or "limited" or "limitation" or "impeder" or "impeders" or "impeding" or "impede" or "impedes" or "impeded" or "represser" or "repressers" or "repressor" or "repressors" or "repressing" or "repress" or "represses" or "repressed" or "repression" or "depressing" or "depress" or "depresses" or "depressed" or "depressor" or	
		"depressors" or "exciter" or "exciters" or "exciting" or "excite" or "excites" or "excited" or "excitement" or "elicitor" or "elicitors" or "eliciting" or "elicit" or "elicits" or "elicited" or "triggering" or "trigger" or "triggers" or "triggered" or "initiator" or "initiators" or "initiating" or "initiate" or "initiates" or "initiated" or "initiation" or "provoker" or "provokers" or "provoking" or "provoke" or "provokes" or "provoked" or "provocation" or "catalyst" or "catalysts" or "catalyzing" or "catalyze" or "catalyzes" or "catalyzed" or "catalysing" or "catalyse" or "catalyses" or "catalysed" or "catalysis" or "invigorator" or "invigorators" or "invigorating" or "invigorate" or "invigorates" or "invigorated" or "invigoration" or "neutralizer" or "neutralizers" or "neutralize" or "neutralizes" or "neutralized" or "neutralizing" or "neutralization" or "neutraliser" or "neutralisers" or "neutralise" or "neutralises" or "neutralised" or "neurtralising" or "neutralisation" or "alter" or "alters" or "altered" or "Altering" or "alteration").ti,ab,kf.	

4	String 2 adj string 3	(("Interleukin-6" or "Interleukin 6" or "IL6" or "IL-6" or "IL 6" or "B-Cell Stimulatory Factor 2" or "B-Cell Stimulatory Factor-2" or "B-Cell Differentiation Factor-2" or "B Cell Differentiation Factor 2" or "BSF-2" or "Hybridoma Growth Factor" or "IFN-beta 2" or "Plasmacytoma Growth Factor" or "Hepatocyte-Stimulating Factor" or "Hepatocyte Stimulating Factor" or "MGI-2" or "Myeloid Differentiation-Inducing Protein" or "Myeloid Differentiation Inducing Protein" or "B-Cell Differentiation Factor" or "B Cell Differentiation Factor" or "Differentiation Factor B-Cell" or "Differentiation Factor B Cell" or "IL-6" or "Interferon beta-2" or "Interferon beta 2" or "beta-2 Interferon" or "B Cell Stimulatory Factor-2" or "B Cell Stimulatory Factor 2" or "Receptor CD126" or "CD126 Antigens" or "Interleukin-1" or "Interleukin 1" or "Interleukin1" or "IL-1" or "IL 1" or "IL1" or "IL1a" or "IL-1a" or "T Helper Factor" or "Lymphocyte-Activating Factor" or "Lymphocyte Activating Factor" or "Epidermal Cell Derived Thymocyte-Activating Factor" or "Epidermal Cell Derived Thymocyte Activating Factor" or "Interleukin I" or "IL-I alpha" or "IL-I beta" or "IL-1alpha" or "Interleukin 1alpha" or "Hematopoietin-1" or "Hematopoietin 1" or "IL-1beta" or "IL-1b" or "IL1b" or "Interleukin 1beta" or "Catabolin" or "Interleukin-18" or "Interleukin 18" or "Interleukin18" or "IFN-gamma-Inducing Factor" or "IL-18" or "Interferon-gamma-Inducing Factor" or "IL18" or "IL 18") adj3 ("Anti-Inflammatories" or "Antiinflammatories" or "Antiinflammatory Agent" or "Antiinflammatory Agents" or "Anti-Inflammatory Agent" or "Immunological Factors" or "Immune Factors" or "Immune Factor" or "Immunological Factor" or "Biomodulators" or "Biomodulator" or "Pro" or "Pro-" or "Procytokine" or "Procytokines" or "Prointerleukin" or "ProIL" or "Proreceptor" or "Pro-cytokine" or "Pro-cytokines" or "Pro-interleukin" or "Pro-IL" or "Pro-receptor" or "Anti" or "Anti-" or "Anticytokine" or "Anticytokines" or "Antiinterleukin" or "AntiIL" or "Antireceptor" or "Anti-cytokine" or "Anti-cytokines" or "Anti-interleukin" or "Anti-IL" or "Anti-receptor" or "Antibody" or "Antibodies" or "Therapeutic" or "Therapeutics" or "Therapy" or "Therapies" or "Small molecule" or "Small molecules" or "Small-molecule" or "Small-molecules" or "Agonist" or "Agonists" or "Antagonist" or "Antagonists" or "Modulate" or "Modulates" or "Modulated" or "Modulator" or "Modulators" or "Modulating" or "Modulation" or "Inhibit" or "Inhibits" or "Inhibited" or "Inhibition" or "Inhibitor" or "Inhibiting" or "Inhibitors" or "Inhibitory" or "Stimulate" or "stimulates" or "stimulated" or "Stimulation" or "Stimulator" or "Stimulators" or "Stimulatory" or "Stimulating" or "Treatment" or "Treat" or "Treats" or "Treated" or "Treating" or "Immunomodulation" or "Immunomodulating" or "Immunomodulator" or "Immunomodulators" or "Immunomodulate" or "Immunomodulates" or "Immunomodulated" or "Immunomodulatory" or "Immunomodulant" or "Immunomodulants" or "Immunemodulation" or "Immunemodulating" or "Immunemodulator" or "Immunemodulators" or "Immunemodulate" or "Immunemodulates" or "Immunemodulated" or "Immunemodulatory" or "Immunemodulant" or "Immunemodulants" or "Immuno-modulation" or "Immuno-modulating" or "Immuno-modulator" or "Immuno-modulators" or "Immuno-modulate" or "Immuno-modulates" or "Immuno-modulated" or "Immuno-modulatory" or "Immuno-modulant" or "Immuno-modulants" or "Immune-modulation" or "Immune-modulating" or "Immune-modulator" or "Immune-modulators" or "Immune-modulate" or "Immune-modulates" or "Immune-modulated" or "Immune-modulatory" or "Immune-modulant" or "Immune-modulants" or "IMiDs" or "Modulant" or "Modulants" or "Immuneregulation" or	98139

		"Immuneregulating" or "Immuneregulator" or "Immuneregulators" or "Immuneregulatory" or "Immuneregulate" or "Immuneregulates" or "Immuneregulated" or "Immunoregulation" or "Immunoregulating" or "Immunoregulator" or "Immunoregulators" or "Immunoregulatory" or "Immunoregulate" or "Immunoregulates" or "Immunoregulated" or "Immune-regulation" or "Immune-regulating" or "Immune-regulator" or "Immune-regulators" or "Immune-regulatory" or "Immune-regulate" or "Immune-regulates" or "Immune-regulated" or "Immuno-regulation" or "Immuno-regulating" or "Immuno-regulator" or "Immuno-regulators" or "Immuno-regulatory" or "Immuno-regulate" or "Immuno-regulates" or "Immuno-regulated" or "Immunestimulation" or "Immunestimulating" or "Immunestimulator" or "Immunestimulators" or "Immunestimulatory" or "Immunestimulate" or "Immunestimulates" or "Immunestimulated" or "immunestimulant" or "immunestimulants" or "Immunostimulation" or "Immunostimulating" or "Immunostimulator" or "Immunostimulators" or "Immunostimulatory" or "Immunostimulate" or "Immunostimulates" or "Immunostimulated" or "immunostimulant" or "immunostimulants" or "Immune-stimulation" or "Immune-stimulating" or "Immune-stimulator" or "Immune-stimulators" or "Immune-stimulatory" or "Immune-stimulate" or "Immune-stimulates" or "Immune-stimulated" or "immune-stimulant" or "immune-stimulants" or "Immuno-stimulation" or "Immuno-stimulating" or "Immuno-stimulator" or "Immuno-stimulators" or "Immuno-stimulatory" or "Immuno-stimulate" or "Immuno-stimulates" or "Immuno-stimulated" or "immuno-stimulant" or "immuno-stimulants" or "Stimulant" or "Stimulants" or "immunesuppression" or "immunesuppressing" or "immunesuppressed" or "immunesuppress" or "immunesuppresses" or "immunesuppressor" or "immunesuppressors" or "immunesuppressant" or "immunesuppressants" or "immunesuppressive" or "immunesuppressives" or "immunosuppression" or "immunosuppressing" or "immunosuppressed" or "immunosuppress" or "immunosuppresses" or "immunosuppressor" or "immunosuppressors" or "immunosuppressant" or "immunosuppressants" or "immunosuppressive" or "immunosuppressives" or "immune-suppression" or "immune-suppressing" or "immune-suppressed" or "immune-suppress" or "immune-suppresses" or "immune-suppressor" or "immune-suppressors" or "immune-suppressant" or "immune-suppressants" or "immune-suppressive" or "immune-suppressives" or "immuno-suppression" or "immuno-suppressing" or "immuno-suppressed" or "immuno-suppress" or "immuno-suppresses" or "immuno-suppressor" or "immuno-suppressors" or "immuno-suppressant" or "immuno-suppressants" or "immuno-suppressive" or "immuno-suppressives" or "Suppressant" or "suppressants" or "Immune-inhibition" or "Immune-inhibiting" or "Immune-inhibit" or "Immune-inhibits" or "Immune-inhibitor" or "Immune-inhibitors" or "Immune-inhibitory" or "Immune-inhibited" or "Immuno-inhibition" or "Immuno-inhibiting" or "Immuno-inhibit" or "Immuno-inhibits" or "Immuno-inhibitor" or "Immuno-inhibitors" or "Immuno-inhibitory" or "Immuno-inhibited" or "Mediate" or "Mediates" or "Mediated" or "Mediator" or "Mediators" or "Mediation" or "Mediating" or "Mediatory" or "Activate" or "Activates" or "Activated" or "Activator" or "Activators" or "Activating" or "Activation" or "Activatory" or "Interpose" or "Interposes" or "Interposed" or "Interposing" or "Interposition" or "regulate" or "regulates" or "regulated" or "Regulating" or "Regulatory" or "regulation" or "regulator" or "regulators" or "promote" or "promotes" or "promoted" or "Promoting" or	

		"Promotion" or "Promotory" or "Promotor" or "Promotors" or "suppress" or "suppresses" or "suppressed" or "suppressing" or "Suppression" or "Suppressor" or "Suppressors" or "Converting" or "convert" or "converted" or "converts" or "convertion" or "converter" or "converters" or "inactivating" or "Inactivate" or "Inactivated" or "inactivates" or "Inactivation" or "inactivatory" or "inactivator" or "inactivators" or "in-activating" or "In-activate" or "In-activated" or "in-activates" or "In-activation" or "Enhancing" or "enhance" or "enhances"	
		or "enhanced" or "enhancer" or "enhancers" or "enhancement" or "block" or "blocks" or "blocked" or "blocking" or "blockade" or "blocker" or "blockers" or "effector" or "effectors" or "effect" or "effects" or "effected" or "effecting" or "affect" or "affects" or "affected" or "affecting" or "changer" or "changers" or "change" or "changes" or "changed" or "Changing" or "adapt" or "adapts" or "adapted" or "Adapting" or "adaptation" or "modifier" or "modifiers" or "modify" or "modifies" or "modified" or "Modifying" or "modification" or "target" or "targets" or "targeting" or "targeted" or "inducer" or "inducers" or "induce" or "induces" or "induced" or "inducing" or "induction" or "restrainer" or "restrainers" or "restraining" or "restrain" or "restrains" or "restrained" or "restricting" or "restrict" or "restricts" or "restricted" or "restriction" or "hindering" or "hinder" or "hinders" or "hindered" or "hindrance" or "hampering" or "hamper" or "hampers" or "hampered" or "retainer" or "retainers" or "retaining" or "retain" or "retains" or "retained" or "retention" or "limiter" or "limiters" or "limiting" or "limit" or "limits" or "limited" or "limitation" or "impeder" or "impeders" or "impeding" or "impede" or "impedes" or "impeded" or "represser" or "repressers" or "repressor" or "repressors" or "repressing" or "repress" or "represses" or "repressed" or "repression" or "depressing" or "depress" or "depresses" or "depressed" or "depressor" or "depressors" or "exciter" or "exciters" or "exciting" or "excite" or "excites" or "excited" or "excitement" or "elicitor" or "elicitors" or "eliciting" or "elicit" or "elicits" or "elicited" or "triggering" or "trigger" or "triggers" or "triggered" or "initiator" or "initiators" or "initiating" or "initiate" or "initiates" or	

		"initiated" or "initiation" or "provoker" or "provokers" or "provoking" or "provoke" or "provokes" or "provoked" or "provocation" or "catalyst" or "catalysts" or "catalyzing" or "catalyze" or "catalyzes" or "catalyzed" or "catalysing" or "catalyse" or "catalyses" or "catalysed" or "catalysis" or "invigorator" or "invigorators" or "invigorating" or "invigorate" or "invigorates" or "invigorated" or "invigoration" or "neutralizer" or "neutralizers" or "neutralize" or "neutralizes" or "neutralized" or "neutralizing" or "neutralization" or "neutraliser" or "neutralisers" or "neutralise" or "neutralises" or "neutralised" or "neurtralising" or "neutralisation" or "alter" or "alters" or "altered" or "Altering" or "alteration")).ti,ab,kf.	
5	Pro and anti tiab	("Anti-Interleukin-6" or "Anti-Interleukin 6" or "Anti-IL6" or "Anti-IL-6" or "Anti-IL 6" or "Anti-BSF-2" or "Anti-MGI-2" or "Anti-IL-6" or "Anti-Interleukin-1" or "Anti-Interleukin 1" or "Anti-Interleukin1" or "Anti-IL-1" or "Anti-IL 1" or "Anti-IL1" or "Anti-IL-1a" or "Anti-IL-1alpha" or "Anti-Interleukin 1alpha" or "Anti-IL-1beta" or "Anti-IL-1b" or "Anti-IL1b" or "Anti-Interleukin 1beta" or "Anti-Interleukin-18" or "Anti-Interleukin 18" or "Anti-IL-18" or "Anti-IL18" or "Anti-IL 18" or "AntiInterleukin-6" or "AntiInterleukin 6" or "AntiIL6" or "AntiIL-6" or "AntiIL 6" or "AntiIL-6" or "AntiInterleukin-1" or "AntiInterleukin 1" or "AntiInterleukin1" or "AntiIL-1" or "AntiIL 1" or "AntiIL1" or "AntiIL1a" or "AntiIL1b" or "AntiInterleukin18" or "AntiIL18" or "Pro-Interleukin-6" or "Pro-Interleukin 6" or "Pro-IL-6" or "Pro-IL 6" or "Pro-IL-6" or "Pro-Interleukin-1" or "Pro-Interleukin 1" or "Pro-IL-1" or "Pro-IL 1" or "Pro-IL1" or "Pro-IL-1alpha" or "Pro-Interleukin 1alpha" or "Pro-IL-1beta" or "Pro-IL-1b" or "Pro-IL1b" or "Pro-Interleukin 1beta" or "Pro-Interleukin-18" or "Pro-Interleukin 18" or "Pro-IL-18" or "Pro-IL18" or "Pro-IL 18" or "ProInterleukin-6" or "ProInterleukin 6" or "ProIL6" or "ProIL-6" or "ProIL 6" or "ProIL-6" or "ProInterleukin-1" or "ProInterleukin 1" or "ProInterleukin1" or "ProIL-1" or "ProIL 1" or "ProIL1" or "ProIL-1alpha" or "ProInterleukin 1alpha" or "ProIL-1beta" or "ProIL1b" or "ProInterleukin 1beta" or "ProInterleukin-18" or "ProInterleukin 18" or "ProInterleukin18" or "ProIL-18" or "ProIL18" or "ProIL 18").ti,ab,kf.	5646
6	Modulation MeSH	exp Interleukin Inhibitors/ or exp Immunomodulating Agents/ or exp Immunosuppressive Agents/ or exp Cytokines/ag, ai	377334
7	Cytokine and Receptor MeSH	exp Interleukin-6/ or exp Receptors, Interleukin-6/ or exp Interleukin-1/ or exp Interleukin-1beta/ or exp Receptors, Interleukin-1/ or exp Interleukin-1alpha/ or exp Interleukin-18/ or exp Receptors, Interleukin-18/	139813
8	String 6 AND 7	6 and 7	8802
9	String 4 OR 5 OR 8	4 or 5 or 8	101648
10	String 1 AND 9	1 and 9	2236

11	Animal string	exp animal experimentation/ or exp models, animal/ or animals/ or exp animal population groups/ or chordata/ or vertebrates/ or exp amphibians/ or exp birds/ or exp fishes/ or exp reptiles/ or mammals/ or primates/ or eutheria/ or exp artiodactyla/ or exp carnivore/ or exp cephalopoda/ or exp cetacea/ or exp chiroptera/ or exp elephants/ or exp hyraxes/ or exp insectivora/ or exp lagomorpha/ or exp marsupialia/ or exp monotremata/ or exp perissodactyla/ or proboscidea mammal/ or exp rodentia/ or exp scandentia/ or exp sirenia/ or exp cingulata/ or haplorhini/ or exp strepsirhini/ or exp platyrrhini/ or exp tarsii/ or catarrhini/ or exp cercopithecidae/ or exp hylobatidae/ or hominidae/ or (rat or rats or animal or animals or mice or "in vivo" or mouse or rabbit or rabbits or murine or pig or pigs or dog or dogs or bovine or fish or vertebrate or vertebrates or cat or cats or rodent or rodents or mammal or mammals or chicken or chickens or monkey or monkeys or sheep or canine or canines or porcine or cattle or bird or birds or hamster or hamsters or primate or primates or cow or cows or chick or horse or horses or avian or avians or calf or swine or swines or xenopus or turkeys or bear or bears or frog or frogs or zebrafish or goat or goats or equine or calves or poultry or macaque or macaques or mole or moles or ovine or lamb or lambs or fishes or diptera or amphibian or amphibians or snake or snakes or ruminant or ruminants or hen or hens or piglet or piglets or feline or felines or simian or simians or laevis or trout or trouts or teleost or teleosts or salmon or salmons or seal or seals or bull or bulls or ewe or ewes or hedgehog or hedgehogs or macaca or macacas or proteus or pigeon or pigeons or bat or bats or duck or ducks or chimpanzee or chimpanzees or baboon or baboons or deer or deers or rana or ranas or carp or carps or heifer or swallow or swallows or lizard or lizards or canis or sow or sows or cynomolgus or quail or quails or reptile or reptiles or turtle or turtles or buffalo or gerbil or gerbils or boar or boars or squirrel or squirrels or oncorhynchus or mus or toad or toads or fowl or fowls or rerio or danio or ara or aras or musculus or tadpole or tadpoles or mulatta or salmo or ram or eagle or eagles or ferret or ferrets or goldfish or catfish or whale or whales or fox or foxes or ape or apes or elephant or elephants or bos or marmoset or marmosets or cod or cods or shark or sharks or wolf or eel or eels or auratus or rattus or zebra or zebras or tilapia or tilapias or gilt or camel or camels or squid or gallus or marsupial or marsupials or vole or voles or fascicularis or ovis or salmonid or salmonids or tiger or tigers or dolphin or dolphins or robin or robins or carpio or opossum or opossums or cyprinus or salamander or salamanders or felis or mink or minks or swan or swans or norvegicus or bufo or torpedo or bass or lamprey or lampreys or sus or python or pythons or tetrapod or tetrapods or shrew or shrews or lion or lions or hog or hogs or songbird or songbirds or oreochromis or starling or starlings or caprine or carassius or owl or owls or newt or newts or papio or scrofa or hare or hares or gorilla or gorillas or flounder or flounders or goose or herring or herrings or therian or buffaloes or canary or sparrow or sparrows or microtus or octopus or troglodytes or tuna or amphibia or chinchilla or chinchillas or ide or oryzias or cervus or kangaroo or kangaroos or armadillo or armadillos or callithrix or "pan troglodytes" or saimiri or cichlid or cichlids or donkey or donkeys or bream or char or chars or finch or raccoon or raccoons or bothrops or anguilla or perch or cricetus or seabird or seabirds or buck or bucks or naja or coturnix or salmonids or geese or minnow or minnows or raptor or raptors or merione or meriones or rodentia or elaphus or amniote or amniotes or elasmobranch or emu or emus or peromyscus or hominid or hominids or bubalus or crotalus or gull or gulls or anas or anura or lemur or lemurs or crow or crows or camelus or gibbon or gibbons or waterfowl or parrot or parrots or eels or cob or stickleback or sticklebacks or columba or mesocricetus or ambystoma or raven or ravens or gadus or penguin	8844118

		or penguins or orangutan or orangutans or sturgeon or sturgeons or cuniculus or aves or virginianus or cephalopod or cephalopods or cebus or sparus or tortoise or tortoises or guttata or morhua or unguiculatus or dogfish or vulpes or mallard or mallards or apodemus or alligator or alligators or oryctolagus or llama or llamas or reindeer or mustela or duckling or ducklings or wolves or sander or amazona or zebu or badger or badgers or dove or doves or ictalurus or capra or capras or equus or camelid or camelids or poecilia or mule or mules or perciformes or salvelinus or labrax or cyprinidae or ariidae or crocodile or crocodiles or fundulus or dicentrarchus or clarias or cercopithecus or chiroptera or alpaca or alpacas or pike or pikes or paralichthys or puma or pumas or didelphis or pisces or macropus or triturus or bison or bisons or epinephelus or gasterosteus or panthera or acipenser or mackerel or mackerels or tamarin or tamarins or ostrich or anolis or vervet or vervets or wallaby or glareolus or beaver or beavers or dromedary or catus or killifish or pimephales or promelas or aotus or phoca or panda or pandas or porpoise or porpoises or myotis or yak or yaks or agkistrodon or vipera or otter or otters or turbot or turbots or squamate or carnivora or mullet or mullets or hawk or hawks or taeniopygia or seahorse or seahorses or "poecilia reticulata" or falcon or falcons or prosimian or prosimians or parus or perca or fingerling or fingerlings or antelope or antelopes or tupaia or passeriformes or sepia or saguinus or coyote or coyotes or pongo or meleagris or reptilia or lepus or psittacine or hagfish or warbler or warblers or "russell s viper" or "russell s vipers" or smolt or smolts or budgerigar or sardine or sardines or cavia or cavias or hyla or pleurodeles or siluriformes or "great tit" or "great tits" or guppy or bonobo or bonobos or rutilus or trichosurus or muridae or phodopus or channa or squalus or lynx or sturnus or petromyzon or vitulina or monodelphis or cuttlefish or adder or adders or lepomis or canaria or gambusia or guppies or xiphophorus or flatfish or koala or koalas or labeo or stingray or stingrays or chelonia or lampetra or spermophilus or crocodilian or "passer domesticus" or sciurus or artiodactyla or ranidae or corvus or necturus or platypus or canaries or bovid or lagopus or trimeresurus or gariepinus or marten or martens or drosophilidae or mugil or sunfish or porcellus or cypriniformes or alouatta or scophthalmus or anser or electrophorus or putorius or iguana or iguanas or lama or lamas or takifugu or circus or eptesicus or flycatcher or galago or galagos or trachemys or lungfish or characiformes or shorebird or shorebirds or giraffe or giraffes or micropterus or scyliorhinus or cichlidae or loligo or porcupine or porcupines or chub or chubs or solea or pleuronectes or hylidae or viperidae or echis or sorex or anchovy or lagomorph or ostriches or vulture or vultures or whitefish or araneus or jird or jirds or tern or esox or drake or drakes or elapidae or gallopavo or chordata or myodes or caretta or serinus or grouse or misgurnus or meles or blackbird or blackbirds or coregonus or bobwhite or bobwhites or heteropneustes or mammoth or mammoths or turdus or rhinella or ateles or characidae or clupea or bungarus or brill or "struthio camelus" or sloth or sloths or pteropus or sculpin or anthropoids or pollock or pollocks or morone or "pan paniscus" or litoria or chipmunk or chipmunks or balaenoptera or marmota or melopsittacus or hyrax or lemming or lemmings or halibut or hylobates or lates or caiman or caimans or sigmodon or stenella or barbel or barbels or sterna or parakeet or parakeets or phocoena or leptodactylus or canidae or buteo or harengus or gopher or gophers or marmot or marmots or gosling or goslings or platichthys or	

gar or gars or sebastes or marsupialia or notophthalmus or gazelle or gazelles or insectivora or paridae or felidae or russula or galliformes or bombina or colobus or echidna or echidnas or seabass or syncerus or plaice or "blue tit" or "blue tits" or pagrus or catfishes or cetacea or barbus or cygnus or ficedula or chamois or colubridae or perches or coelacanth or fitch or urodela or cynops or martes or halichoerus or aix or salmonidae or leuciscus or magpie or magpies or silurus or whiting or whitings or anseriformes or colinus or rhea or chlorocebus or octodon or acinonyx or mouflon or mouflons or ibex or tetraodon or bufonidae or equidae or jackal or cephalopoda or dendroaspis or glama or muskrat or muskrats or sable or sables or wildebeest or streptopelia or albifrons or vespertilionidae or woodpecker or woodpeckers or muntjac or muntjacs or archosaur or branta or cricetulus or megalobrama or poeciliidae or desmodus or snakehead or snakeheads or tench or teal or teals or bandicoot or bandicoots or apteronotus or phyllostomidae or crocidura or buzzard or buzzards or larimichthys or cercocebus or pipistrellus or erithacus or impala or impalas or rousettus or haddock or haddocks or tinca or ratite or calidris or cynoglossus or hypophthalmichthys or bullock or bullocks or dromedaries or alectoris or filly or salamandra or cingulata or bitis or grus or ammodytes or macaw or macaws or hypoleuca or sapajus or cyprinodontiformes or hippopotamus or pelophylax or capybara or capybaras or weasel or weasels or cairina or cynomys or lutra or cockatoo or cockatoos or lachesis or lagomorpha or rupicapra or daboia or "orang utan" or "orang utans" or platyrrhini or charadriiformes or micrurus or psittaciformes or spalax or loris or mustelidae or sylvilagus or vitticeps or cockatiel or mustelus or cottus or erythrocebus or dipodomys or platessa or callicebus or loricariidae or catostomus or cuneata or cyanistes or cyprinodon or sigmodontinae or elasmobranchii or trichechus or sauropsid or xenarthra or dormouse or perissodactyla or nautilus or cirrhinus or gulo or gulos or tragelaphus or merula or numida or sciaenidae or cerastes or sciuridae or gibbosus or octopuses or eland or elands or phyllomedusa or pogona or walrus or agamidae or leptodactylidae or ridibundus or leontopithecus or anteater or anteaters or pelodiscus or cebidae or columbianus or "pelteobagrus fulvidraco" or hominoidea or mandrillus or "zonotrichia leucophrys" or agama or gobiocypris or "bearded dragon" or "bearded dragons" or sarotherodon or talpa or discoglossus or hagfishes or sphenodon or gudgeon or amphiuma or aythya or tenrec or tenrec or hominidae or risoria or salamandridae or camelidae or columbiformes or latimeria or plover or plovers or afrotheria or "falco sparverius" or polecat or polecats or crotalinae or salvadora or tarsier or lucioperca or anchovies or lungfishes or terrapin or "dromaius novaehollandiae" or lateolabrax or eigenmannia or pelamis or theropithecus or murinae or gander or gymnotus or pseudacris or gymnophiona or gymnotiformes or laticauda or falconiformes or dugong or dugongs or pintail or pintails or rook or rooks or lasiurus or catshark or catsharks or micropogonias or "red junglefowl" or paddlefish or ophiophagus or hollandicus or nymphicus or pimelodidae or aepyceros or cobitidae or strigiformes or cobitis or dormice or alytes or calloselasma or guanaco or guanacos or phasianidae or "round goby" or trichogaster or catarrhini or eelpout or eelpouts or galaxias or gaur or pungitius or suslik or susliks or flatfishes or percidae or caprinae or todarodes or osmerus or ameiurus or anthropoidea or "castor canadensis" or pouting or poutings or tetraodontiformes or arvicolinae or siamang or siamangs or "castor fiber" or nomascus or "red knot" or "red knots" or syngnathidae or iguanidae or eretmochelys or ursidae or callimico or columbidae or microhylidae or anaxyrus or menidia or pipistrelle or greylag or pipidae or scandentia or bowfin or bowfins or dendrobatidae or zenaida or bushbaby or harrier or harriers or macropodidae or pygerythrus or clupeidae or odorrana or corvidae or

		jerboa or jerboas or canutus or hylobatidae or clupeiformes or "great cormorant" or "great cormorants" or scorpaeniformes or chondrostean or garfish or proboscidea or psetta or diapsid or serotinus or tetrao or walruses or carcharhiniformes or leucoraja or pumpkinseed or dosidicus or acipenseriformes or daubentonii or emberizidae or gadiformes or hyraxes or stizostedion or wolverine or wolverines or lissotriton or acanthurus or centrarchidae or gloydius or laurasiatheria or limosa or psittacula or leporidae or proteidae or zander or zanders or arapaima or bagridae or cyprinodontidae or mithun or pandion or jackdaw or jackdaws or procyonidae or carus or jaculus or salmoniformes or "common sole" or "common soles" or protobothrops or calamita or brachyteles or trionyx or turdidae or boidae or luscinia or pugnax or euarchontoglires or saithe or saithes or symphalangus or aardvark or aardvarks or oystercatcher or oystercatchers or arius or corydoras or poacher or poachers or aurochs or cebuella or crecca or lemuridae or sirenia or lemmus or perdix or glires or lepidosaur or muskox or deinagkistrodon or pholidota or holocephali or cercopithecinae or clariidae or agapornis or doryteuthis or tyrannidae or dicroglossidae or godwit or godwits or monedula or pongidae or atheriniformes or colobinae or lophocebus or atelidae or cottidae or leucopsis or acanthuridae or didelphimorphia or elver or elvers or lapponica or dermoptera or "european hake" or "european hakes" or gerbillinae or banteng or hartebeest or hartebeests or hogget or haematopus or "anguis fragilis" or "grey heron" or "grey herons" or "blue whiting" or "blue whitings" or furnariidae or macrovipera or esocidae or lapwing or lapwings or mylopharyngodon or wallabia or beloniformes or potoroo or potoroos or "athene noctua" or pleuronectidae or bushbabies or muscicapidae or alligatoridae or fuligula or "bush baby" or guineafowl or spoonbill or spoonbills or viverridae or catostomidae or zebrafishes or ibexes or vendace or estrildidae or monotremata or sepiella or ambystomatidae or shelduck or shelducks or treeshrew or treeshrews or hoplobatrachus or pochard or hoolock or hoolocks or lynxes or antilope or antilopes or blackbuck or blackbucks or cricetinae or paramisgurnus or skylark or skylarks or soleidae or allobates or "northern wheatear" or "northern wheatears" or pitheciidae or takin or theria or vanellus or galaxiidae or lorisidae or ostralegus or palaeognathae or "stone loach" or alauda or callitrichinae or caniformia or duttaphrynus or ictaluridae or osteoglossiformes or poultries or curema or "ruddy turnstone" or "ruddy turnstones" or sheatfish or sunfishes or centropomidae or hemachatus or platalea or thamnophilidae or "song thrush" or atherinopsidae or siluridae or tadorna or chroicocephalus or ermine or ermines or gavialis or ruff or tupaiidae or diprotodontia or hyaenidae or antilopinae or crocodylidae or herpestidae or hippopotamidae or "northern shoveler" or "round gobies" or cheirogaleidae or indriidae or fundulidae or pythonidae or rhynchocephalia or anodorhynchus or "red-backed shrike" or "red-backed shrikes" or triakidae or phalangeridae or aoudad or boreoeutheria or "eurasian jay" or "eurasian jays" or feliformia or haplorhini or osteoglossidae or paenungulata or struthioniformes or ferina or sanderling or sanderlings or spheniscidae or cuttlefishes or cygnet or dasycneme or gadwall or gadwalls or "pelobates fuscus" or wryneck or wrynecks or afrosoricida or culaea or "dover sole" or "dover soles" or paralichthyidae or passeridae or osteolaemus or "song thrushes" or bluethroat or bluethroats or hydrophiidae or megrim or mephitidae or strepsirhini or tomistoma or epidalea or osmeriformes or "bush babies" or tarsiiform or atelinae or bufotes or "eurasian coot" or "eurasian coots" or galagidae or geopelia or philomachus or	

		tubulidentata or bombinatoridae or pelobatidae or tachysurus or ailuridae or woodlark or woodlarks or alcelaphinae or redshank or redshanks or salientia or "sand smelt" or "sand smelts" or woodmice or woodmouse or dasyproctidae or "eurasian wigeon" or "eurasian wigeons" or garganey or garganeys or "lemon sole" or "lemon soles" or "common dab" or "common dabs" or graylag or graylags or leucorodia or osphronemidae or bewickii or "common moorhen" or "common moorhens" or decapodiformes or gobbler or gobblers or odontophoridae or paddlefishes or eutheria or salmonine or esociformes or "eurasian woodcock" or "eurasian woodcocks" or "european smelt" or "european smelts" or goldfishes or tenches or tyranni or "common chaffinch" or "common chaffinchs" or "common redstart" or "common redstarts" or "common roach" or "common roachs" or "great knot" or "great knots" or potoroidae or alytidae or coregonine or dipteral or leveret or "poeciliopsis gracilis" or amphiumidae or batrachoidiformes or "bighead goby" or heteropneustidae or lullula or "norway pout" or "norway pouts" or sipunculida or dogfishes or sebastidae or tarsiidae or alethinophidia or "common nase" or "common nases" or "common sandpiper" or "common sandpipers" or "eurasian blackcap" or "eurasian blackcaps" or pterocnemia or syngnathiformes or "common chaffinches" or eupleridae or octopodiformes or phascolarctidae or scophthalmidae or "starry smooth-hound" or "starry smooth-hounds" or whitefishes or cuniculidae or "european sprat" or "european sprats" or "rosy bitterling" or "rosy bitterlings" or "common dace" or "common daces" or "lesser weever" or "lesser weevers" or scaldfish or "water rail" or "water rails" or alouattinae or centrarchiformes or "common whitethroat" or "common whitethroats" or gavialidae or "grey gurnard" or "grey gurnards" or lateolabracidae or rheiformes or "tub gurnard" or "tub gurnards" or "common chiffchaff" or "common chiffchaffs" or garfishes or "lesser whitethroat" or "lesser whitethroats" or myoxidae or seabasses or spariformes or umbridae or "yellow boxfish" or anabantiformes or aotidae or "common bleak" or "common bleaks" or "common rudd" or "common rudds" or "greater pipefish" or hapale or nandiniidae or "stone loaches" or whinchat or whinchats or acanthuriformes or "brotula barbata" or "common ling" or "common lings" or "common roaches" or cottonrat or cottonrats or douroucoulis or dromaiidae or fitches or fitchew or galaxiiformes or laprine or saimiriinae or solenette or tarsii or "tompot blenny" or "common dragonet" or "common dragonets" or "longspined bullhead" or "longspined bullheads" or monotremate or monotremates or pempheriformes or perdicinae or presbytini or smegmamorpha or "bighead gobies" or "carangaria incertae sedis" or coiidae or "fivebeard rockling" or foulmart or foumart or grasskeet or "greater pipefishes" or ibices or millionfish or muguliformes or "norwegian topknot" or peewit or "red sea sailfin tang" or rupicapras or sheatfishes or "tompot blennies" or "twait shad" or "yellow boxfishes").ti,ab,kf.	
12	String 10 AND 11	10 and 11	**1064**

Supplementary Table 2. Search string EMBASE.

Supplementary Table 2. EMBASE (OVID) search strings			
String	**String name**	**Terms**	**HITS (14-11-2023)**
1	Atherosclerosis	exp atherosclerosis/ or "Atherosclerosis".ti,ab,kf. or "Atheroscleroses".ti,ab,kf. or "Atherogenesis".ti,ab,kf. or "Plaque Atherosclerotic".ti,ab,kf. or "Plaques Atherosclerotic".ti,ab,kf. or "Atherosclerotic Plaques".ti,ab,kf. or "Atherosclerotic	336612

		Plaque".ti,ab,kf. or "Fatty Streak Arterial".ti,ab,kf. or "Arterial Fatty Streaks".ti,ab,kf. or "Fibroatheroma".ti,ab,kf. or "Fibroatheromas".ti,ab,kf. or "Fibroatheromatous".ti,ab,kf. or "Atheroma".ti,ab,kf. or "Atheromas".ti,ab,kf. or "Atheromatous".ti,ab,kf.	
2	Cytokine and Receptor tiab	("Interleukin-6" or "Interleukin 6" or "IL6" or "IL-6" or "IL 6" or "B-Cell Stimulatory Factor 2" or "B-Cell Stimulatory Factor-2" or "B-Cell Differentiation Factor-2" or "B Cell Differentiation Factor 2" or "BSF-2" or "Hybridoma Growth Factor" or "IFN-beta 2" or "Plasmacytoma Growth Factor" or "Hepatocyte-Stimulating Factor" or "Hepatocyte Stimulating Factor" or "MGI-2" or "Myeloid Differentiation-Inducing Protein" or "Myeloid Differentiation Inducing Protein" or "B-Cell Differentiation Factor" or "B Cell Differentiation Factor" or "Differentiation Factor B-Cell" or "Differentiation Factor B Cell" or "IL-6" or "Interferon beta-2" or "Interferon beta 2" or "beta-2 Interferon" or "B Cell Stimulatory Factor-2" or "B Cell Stimulatory Factor 2" or "Receptor CD126" or "CD126 Antigens" or "Interleukin-1" or "Interleukin 1" or "Interleukin1" or "IL-1" or "IL 1" or "IL1" or "IL1a" or "IL-1a" or "T Helper Factor" or "Lymphocyte-Activating Factor" or "Lymphocyte Activating Factor" or "Epidermal Cell Derived Thymocyte-Activating Factor" or "Epidermal Cell Derived Thymocyte Activating Factor" or "Interleukin I" or "IL-I alpha" or "IL-I beta" or "IL-1alpha" or "Interleukin 1alpha" or "Hematopoietin-1" or "Hematopoietin 1" or "IL-1beta" or "IL-1b" or "IL1b" or "Interleukin 1beta" or "Catabolin" or "Interleukin-18" or "Interleukin 18" or "Interleukin18" or "IFN-gamma-Inducing Factor" or "IL-18" or "Interferon-gamma-Inducing Factor" or "IL18" or "IL 18").ti,ab,kf.	406374
3	Modulation tiab	("Anti-Inflammatories" or "Antiinflammatories" or "Antiinflammatory Agent" or "Antiinflammatory Agents" or "Anti-Inflammatory Agent" or "Immunological Factors" or "Immune Factors" or "Immune Factor" or "Immunological Factor" or "Biomodulators" or "Biomodulator" or "Pro" or "Pro-" or "Procytokine" or "Procytokines" or "Prointerleukin" or "ProIL" or "Proreceptor" or "Pro-cytokine" or "Pro-cytokines" or "Pro-interleukin" or "Pro-IL" or "Pro-receptor" or "Anti" or "Anti-" or "Anticytokine" or "Anticytokines" or "Antiinterleukin" or "AntiIL" or "Antireceptor" or "Anti-cytokine" or "Anti-cytokines" or "Anti-interleukin" or "Anti-IL" or "Anti-receptor" or "Antibody" or "Antibodies" or "Therapeutic" or "Therapeutics" or "Therapy" or "Therapies" or "Small molecule" or "Small molecules" or "Small-molecule" or "Small-molecules" or "Agonist" or "Agonists" or "Antagonist" or "Antagonists" or "Modulate" or "Modulates" or "Modulated" or "Modulator" or "Modulators" or "Modulating" or "Modulation" or "Inhibit" or "Inhibits" or "Inhibited" or "Inhibition" or "Inhibitor" or "Inhibiting" or "Inhibitors" or "Inhibitory" or "Stimulate" or "stimulates" or "stimulated" or "Stimulation" or "Stimulator" or "Stimulators" or "Stimulatory" or "Stimulating" or "Treatment" or "Treat" or "Treats" or "Treated" or "Treating" or "Immunomodulation" or "Immunomodulating" or "Immunomodulator" or "Immunomodulators" or "Immunomodulate" or "Immunomodulates" or "Immunomodulated" or "Immunomodulatory" or "Immunomodulant" or "Immunomodulants" or "Immunemodulation" or "Immunemodulating" or "Immunemodulator" or "Immunemodulators" or "Immunemodulate" or "Immunemodulates" or "Immunemodulated" or "Immunemodulatory" or "Immunemodulant" or "Immunemodulants" or "Immuno-	26166861

		modulation" or "Immuno-modulating" or "Immuno-modulator" or "Immuno-modulators" or "Immuno-modulate" or "Immuno-modulates" or "Immuno-modulated" or "Immuno-modulatory" or "Immuno-modulant" or "Immuno-modulants" or "Immune-modulation" or "Immune-modulating" or "Immune-modulator" or "Immune-modulators" or "Immune-modulate" or "Immune-modulates" or "Immune-modulated" or "Immune-modulatory" or "Immune-modulant" or "Immune-modulants" or "IMiDs" or "Modulant" or "Modulants" or "Immuneregulation" or "Immuneregulating" or "Immuneregulator" or "Immuneregulators" or "Immuneregulatory" or "Immuneregulate" or "Immuneregulates" or "Immuneregulated" or "Immunoregulation" or "Immunoregulating" or "Immunoregulator" or "Immunoregulators" or "Immunoregulatory" or "Immunoregulate" or "Immunoregulates" or "Immunoregulated" or "Immune-regulation" or "Immune-regulating" or "Immune-regulator" or "Immune-regulators" or "Immune-regulatory" or "Immune-regulate" or "Immune-regulates" or "Immune-regulated" or "Immuno-regulation" or "Immuno-regulating" or "Immuno-regulator" or "Immuno-regulators" or "Immuno-regulatory" or "Immuno-regulate" or "Immuno-regulates" or "Immuno-regulated" or "Immunestimulation" or "Immunestimulating" or "Immunestimulator" or "Immunestimulators" or "Immunestimulatory" or "Immunestimulate" or "Immunestimulates" or "Immunestimulated" or "immunestimulant" or "immunestimulants" or "Immunostimulation" or "Immunostimulating" or "Immunostimulator" or "Immunostimulators" or "Immunostimulatory" or "Immunostimulate" or "Immunostimulates" or "Immunostimulated" or "immunostimulant" or "immunostimulants" or "Immune-stimulation" or "Immune-stimulating" or "Immune-stimulator" or "Immune-stimulators" or "Immune-stimulatory" or "Immune-stimulate" or "Immune-stimulates" or "Immune-stimulated" or "immune-stimulant" or "immune-stimulants" or "Immuno-stimulation" or "Immuno-stimulating" or "Immuno-stimulator" or "Immuno-stimulators" or "Immuno-stimulatory" or "Immuno-stimulate" or "Immuno-stimulates" or "Immuno-stimulated" or "immuno-stimulant" or "immuno-stimulants" or "Stimulant" or "Stimulants" or "immunesuppression" or "immunesuppressing" or "immunesuppressed" or "immunesuppress" or "immunesuppresses" or "immunesuppressor" or "immunesuppressors" or "immunesuppressant" or	

		"immunesuppressants" or "immunesuppressive" or "immunesuppressives" or "immunosuppression" or "immunosuppressing" or "immunosuppressed" or "immunosuppress" or "immunosuppresses" or "immunosuppressor" or "immunosuppressors" or "immunosuppressant" or "immunosuppressants" or "immunosuppressive" or "immunosuppressives" or "immune-suppression" or "immune-suppressing" or "immune-suppressed" or "immune-suppress" or "immune-suppresses" or "immune-suppressor" or "immune-suppressors" or "immune-suppressant" or "immune-suppressants" or "immune-suppressive" or "immune-suppressives" or "immuno-suppression" or "immuno-suppressing" or "immuno-suppressed" or "immuno-suppress" or "immuno-suppresses" or "immuno-suppressor" or "immuno-suppressors" or "immuno-suppressant" or "immuno-suppressants" or "immuno-suppressive" or "immuno-suppressives" or "Suppressant" or "suppressants" or "Immune-inhibition" or "Immune-inhibiting" or "Immune-inhibit" or "Immune-inhibits" or "Immune-inhibitor" or "Immune-inhibitors" or "Immune-inhibitory" or "Immune-inhibited" or "Immuno-inhibition" or "Immuno-inhibiting" or "Immuno-inhibit" or "Immuno-inhibits" or "Immuno-inhibitor" or "Immuno-inhibitors" or "Immuno-inhibitory" or "Immuno-inhibited" or "Mediate" or "Mediates" or "Mediated" or "Mediator" or "Mediators" or "Mediation" or "Mediating" or "Mediatory" or "Activate" or "Activates" or "Activated" or "Activator" or "Activators" or "Activating" or "Activation" or "Activatory" or "Interpose" or "Interposes" or "Interposed" or "Interposing" or "Interposition" or "regulate" or "regulates" or "regulated" or "Regulating" or "Regulatory" or "regulation" or "regulator" or "regulators" or "promote" or "promotes" or "promoted" or "Promoting" or "Promotion" or "Promotory" or "Promotor" or "Promotors" or "suppress" or "suppresses" or "suppressed" or "suppressing" or "Suppression" or "Suppressor" or "Suppressors" or "Converting" or "convert" or "converted" or "converts" or "convertion" or "converter" or "converters" or "inactivating" or "Inactivate" or "Inactivated" or "inactivates" or "Inactivation" or "inactivatory" or "inactivator" or "inactivators" or "in-activating" or "In-activate" or "In-activated" or "in-activates" or "In-activation" or "Enhancing" or "enhance" or "enhances" or "enhanced" or "enhancer" or "enhancers" or "enhancement" or "block" or "blocks" or "blocked" or "blocking" or "blockade" or "blocker" or "blockers" or "effector" or "effectors" or "effect" or "effects" or "effected" or "effecting" or "affect" or "affects" or "affected" or "affecting" or "changer" or "changers" or "change" or "changes" or "changed" or "Changing" or "adapt" or "adapts" or "adapted" or "Adapting" or "adaptation" or "modifier" or "modifiers" or "modify" or "modifies" or "modified" or "Modifying" or "modification" or "target" or "targets" or "targeting" or "targeted" or "inducer" or "inducers" or "induce" or "induces" or "induced" or "inducing" or "induction" or "restrainer" or "restrainers" or "restraining" or "restrain" or "restrains" or "restrained" or "restricting" or "restrict" or "restricts" or "restricted" or "restriction" or "hindering" or "hinder" or "hinders" or "hindered" or "hindrance" or "hampering" or "hamper" or "hampers" or "hampered" or "retainer" or "retainers" or "retaining" or "retain" or "retains" or "retained" or "retention" or "limiter" or "limiters" or "limiting" or "limit" or "limits" or "limited" or "limitation" or "impeder" or "impeders" or "impeding" or "impede" or "impedes" or "impeded" or "represser" or "repressers" or "repressor" or "repressors" or "repressing" or "repress" or "represses" or "repressed" or	

		"repression" or "depressing" or "depress" or "depresses" or "depressed" or "depressor" or "depressors" or "exciter" or "exciters" or "exciting" or "excite" or "excites" or "excited" or "excitement" or "elicitor" or "elicitors" or "eliciting" or "elicit" or "elicits" or "elicited" or "triggering" or "trigger" or "triggers" or "triggered" or "initiator" or "initiators" or "initiating" or "initiate" or "initiates" or "initiated" or "initiation" or "provoker" or "provokers" or "provoking" or "provoke" or "provokes" or "provoked" or "provocation" or "catalyst" or "catalysts" or "catalyzing" or "catalyze" or "catalyzes" or "catalyzed" or "catalysing" or "catalyse" or "catalyses" or "catalysed" or "catalysis" or "invigorator" or "invigorators" or "invigorating" or "invigorate" or "invigorates" or "invigorated" or "invigoration" or "neutralizer" or "neutralizers" or "neutralize" or "neutralizes" or "neutralized" or "neutralizing" or "neutralization" or "neutraliser" or "neutralisers" or "neutralise" or "neutralises" or "neutralised" or "neurtralising" or "neutralisation" or "alter" or "alters" or "altered" or "Altering" or "alteration").ti,ab,kf.	
4	String 2 adj string 3	(("Interleukin-6" or "Interleukin 6" or "IL6" or "IL-6" or "IL 6" or "B-Cell Stimulatory Factor 2" or "B-Cell Stimulatory Factor-2" or "B-Cell Differentiation Factor-2" or "B Cell Differentiation Factor 2" or "BSF-2" or "Hybridoma Growth Factor" or "IFN-beta 2" or "Plasmacytoma Growth Factor" or "Hepatocyte-Stimulating Factor" or "Hepatocyte Stimulating Factor" or "MGI-2" or "Myeloid Differentiation-Inducing Protein" or "Myeloid Differentiation Inducing Protein" or "B-Cell Differentiation Factor" or "B Cell Differentiation Factor" or "Differentiation Factor B-Cell" or "Differentiation Factor B Cell" or "IL-6" or "Interferon beta-2" or "Interferon beta 2" or "beta-2 Interferon" or "B Cell Stimulatory Factor-2" or "B Cell Stimulatory Factor 2" or "Receptor CD126" or "CD126 Antigens" or "Interleukin-1" or "Interleukin 1" or "Interleukin1" or "IL-1" or "IL 1" or "IL1" or "IL1a" or "IL-1a" or "T Helper Factor" or "Lymphocyte-Activating Factor" or "Lymphocyte Activating Factor" or "Epidermal Cell Derived Thymocyte-Activating Factor" or "Epidermal Cell Derived Thymocyte Activating Factor" or "Interleukin I" or "IL-I alpha" or "IL-I beta" or "IL-1alpha" or "Interleukin 1alpha" or "Hematopoietin-1" or "Hematopoietin 1" or "IL-1beta" or "IL-1b" or "IL1b" or "Interleukin 1beta" or "Catabolin" or "Interleukin-18" or "Interleukin 18" or "Interleukin18" or "IFN-gamma-Inducing Factor" or "IL-18" or "Interferon-gamma-Inducing Factor" or "IL18" or "IL 18") adj3 ("Anti-Inflammatories" or "Antiinflammatories" or "Antiinflammatory Agent" or "Antiinflammatory Agents" or "Anti-Inflammatory Agent" or "Immunological Factors" or "Immune Factors" or "Immune Factor" or "Immunological Factor" or "Biomodulators" or "Biomodulator" or "Pro" or "Pro-" or "Procytokine" or "Procytokines" or "Prointerleukin" or "ProIL" or "Proreceptor" or "Pro-cytokine" or "Pro-cytokines" or "Pro-interleukin" or "Pro-IL" or "Pro-receptor" or "Anti" or "Anti-" or "Anticytokine" or "Anticytokines" or "Antiinterleukin" or "AntiIL" or "Antireceptor" or "Anti-cytokine" or "Anti-cytokines" or "Anti-interleukin" or "Anti-IL" or "Anti-receptor" or "Antibody" or "Antibodies" or "Therapeutic" or "Therapeutics" or "Therapy" or "Therapies" or "Small molecule" or "Small molecules" or "Small-molecule" or "Small-molecules" or "Agonist" or "Agonists" or "Antagonist" or "Antagonists" or	134095

		"Modulate" or "Modulates" or "Modulated" or "Modulator" or "Modulators" or "Modulating" or "Modulation" or "Inhibit" or "Inhibits" or "Inhibited" or "Inhibition" or "Inhibitor" or "Inhibiting" or "Inhibitors" or "Inhibitory" or "Stimulate" or "stimulates" or "stimulated" or "Stimulation" or "Stimulator" or "Stimulators" or "Stimulatory" or "Stimulating" or "Treatment" or "Treat" or "Treats" or "Treated" or "Treating" or "Immunomodulation" or "Immunomodulating" or "Immunomodulator" or "Immunomodulators" or "Immunomodulate" or "Immunomodulates" or "Immunomodulated" or "Immunomodulatory" or "Immunomodulant" or "Immunomodulants" or "Immunemodulation" or "Immunemodulating" or "Immunemodulator" or "Immunemodulators" or "Immunemodulate" or "Immunemodulates" or "Immunemodulated" or "Immunemodulatory" or "Immunemodulant" or "Immunemodulants" or "Immuno-modulation" or "Immuno-modulating" or "Immuno-modulator" or "Immuno-modulators" or "Immuno-modulate" or "Immuno-modulates" or "Immuno-modulated" or "Immuno-modulatory" or "Immuno-modulant" or "Immuno-modulants" or "Immune-modulation" or "Immune-modulating" or "Immune-modulator" or "Immune-modulators" or "Immune-modulate" or "Immune-modulates" or "Immune-modulated" or "Immune-modulatory" or "Immune-modulant" or "Immune-modulants" or "IMiDs" or "Modulant" or "Modulants" or "Immuneregulation" or "Immuneregulating" or "Immuneregulator" or "Immuneregulators" or "Immuneregulatory" or "Immuneregulate" or "Immuneregulates" or "Immuneregulated" or "Immunoregulation" or "Immunoregulating" or "Immunoregulator" or "Immunoregulators" or "Immunoregulatory" or "Immunoregulate" or "Immunoregulates" or "Immunoregulated" or "Immune-regulation" or "Immune-regulating" or "Immune-regulator" or "Immune-regulators" or "Immune-regulatory" or "Immune-regulate" or "Immune-regulates" or "Immune-regulated" or "Immuno-regulation" or "Immuno-regulating" or "Immuno-regulator" or "Immuno-regulators" or "Immuno-regulatory" or "Immuno-regulate" or "Immuno-regulates" or "Immuno-regulated" or "Immunestimulation" or "Immunestimulating" or "Immunestimulator" or "Immunestimulators" or "Immunestimulatory" or "Immunestimulate" or "Immunestimulates" or "Immunestimulated" or "immunestimulant" or "immunestimulants" or "Immunostimulation" or "Immunostimulating" or "Immunostimulator" or "Immunostimulators" or "Immunostimulatory" or "Immunostimulate" or "Immunostimulates" or "Immunostimulated" or "immunostimulant" or "immunostimulants" or "Immune-stimulation" or "Immune-stimulating" or "Immune-stimulator" or "Immune-stimulators" or "Immune-stimulatory" or "Immune-stimulate" or "Immune-stimulates" or "Immune-stimulated" or "immune-stimulant" or "immune-stimulants" or "Immuno-stimulation" or "Immuno-stimulating" or "Immuno-stimulator" or "Immuno-stimulators" or "Immuno-stimulatory" or "Immuno-stimulate" or "Immuno-stimulates" or "Immuno-stimulated" or "immuno-stimulant" or "immuno-stimulants" or "Stimulant" or "Stimulants" or "immunesuppression" or "immunesuppressing" or "immunesuppressed" or "immunesuppress" or "immunesuppresses" or "immunesuppressor" or "immunesuppressors" or "immunesuppressant" or "immunesuppressants" or "immunesuppressive" or	

		"immunesuppressives" or "immunosuppression" or "immunosuppressing" or "immunosuppressed" or "immunosuppress" or "immunosuppresses" or "immunosuppressor" or "immunosuppressors" or "immunosuppressant" or "immunosuppressants" or "immunosuppressive" or "immunosuppressives" or "immune-suppression" or "immune-suppressing" or "immune-suppressed" or "immune-suppress" or "immune-suppresses" or "immune-suppressor" or "immune-suppressors" or "immune-suppressant" or "immune-suppressants" or "immune-suppressive" or "immune-suppressives" or "immuno-suppression" or "immuno-suppressing" or	
		immuno-suppressed or "immuno-suppress" or "immuno-suppresses" or "immuno-suppressor" or "immuno-suppressors" or "immuno-suppressant" or "immuno-suppressants" or "immuno-suppressive" or "immuno-suppressives" or "Suppressant" or "suppressants" or "Immune-inhibition" or "Immune-inhibiting" or "Immune-inhibit" or "Immune-inhibits" or "Immune-inhibitor" or "Immune-inhibitors" or "Immune-inhibitory" or "Immune-inhibited" or "Immuno-inhibition" or "Immuno-inhibiting" or "Immuno-inhibit" or "Immuno-inhibits" or "Immuno-inhibitor" or "Immuno-inhibitors" or "Immuno-inhibitory" or "Immuno-inhibited" or "Mediate" or "Mediates" or "Mediated" or "Mediator" or "Mediators" or "Mediation" or "Mediating" or "Mediatory" or "Activate" or "Activates" or "Activated" or "Activator" or "Activators" or "Activating" or "Activation" or "Activatory" or "Interpose" or "Interposes" or "Interposed" or "Interposing" or "Interposition" or "regulate" or "regulates" or "regulated" or "Regulating" or "Regulatory" or "regulation" or "regulator" or "regulators" or "promote" or "promotes" or "promoted" or "Promoting" or "Promotion" or "Promotory" or "Promotor" or "Promotors" or "suppress" or "suppresses" or "suppressed" or "suppressing" or "Suppression" or "Suppressor" or "Suppressors" or "Converting" or "convert" or "converted" or "converts" or "convertion" or "converter" or "converters" or "inactivating" or "Inactivate" or "Inactivated" or "inactivates" or "Inactivation" or "inactivatory" or "inactivator" or "inactivators" or "in-activating" or "In-activate" or "In-activated" or "in-activates" or "In-activation" or "Enhancing" or "enhance" or "enhances" or "enhanced" or "enhancer" or "enhancers" or "enhancement" or "block" or "blocks" or "blocked" or "blocking" or "blockade" or "blocker" or "blockers" or "effector" or "effectors" or "effect" or "effects" or "effected" or "effecting" or	

		"affect" or "affects" or "affected" or "affecting" or "changer" or "changers" or "change" or "changes" or "changed" or "Changing" or "adapt" or "adapts" or "adapted" or "Adapting" or "adaptation" or "modifier" or "modifiers" or "modify" or "modifies" or "modified" or "Modifying" or "modification" or "target" or "targets" or "targeting" or "targeted" or "inducer" or "inducers" or "induce" or "induces" or "induced" or "inducing" or "induction" or "restrainer" or "restrainers" or "restraining" or "restrain" or "restrains" or "restrained" or "restricting" or "restrict" or "restricts" or "restricted" or "restriction" or "hindering" or "hinder" or "hinders" or "hindered" or "hindrance" or "hampering" or "hamper" or "hampers" or "hampered" or "retainer" or "retainers" or "retaining" or "retain" or "retains" or "retained" or "retention" or "limiter" or "limiters" or "limiting" or "limit" or "limits" or "limited" or "limitation" or "impeder" or "impeders" or "impeding" or "impede" or "impedes" or "impeded" or "represser" or "repressers" or "repressor" or "repressors" or "repressing" or "repress" or "represses" or "repressed" or "repression" or "depressing" or "depress" or "depresses" or "depressed" or "depressor" or "depressors" or "exciter" or "exciters" or "exciting" or "excite" or "excites" or "excited" or "excitement" or "elicitor" or "elicitors" or "eliciting" or "elicit" or "elicits" or "elicited" or "triggering" or "trigger" or "triggers" or "triggered" or "initiator" or "initiators" or "initiating" or "initiate" or "initiates" or "initiated" or "initiation" or "provoker" or "provokers" or "provoking" or "provoke" or "provokes" or "provoked" or "provocation" or "catalyst" or "catalysts" or "catalyzing" or "catalyze" or "catalyzes" or "catalyzed" or "catalysing" or "catalyse" or "catalyses" or "catalysed" or "catalysis" or "invigorator" or "invigorators" or "invigorating" or "invigorate" or "invigorates" or "invigorated" or "invigoration" or "neutralizer" or "neutralizers" or "neutralize" or "neutralizes" or "neutralized" or "neutralizing" or "neutralization" or "neutraliser" or "neutralisers" or "neutralise" or "neutralises" or "neutralised" or "neurtralising" or "neutralisation" or "alter" or "alters" or "altered" or "Altering" or "alteration")).ti,ab,kf.	
5	Pro and anti tiab	("Anti-Interleukin-6" or "Anti-Interleukin 6" or "Anti-IL6" or "Anti-IL-6" or "Anti-IL 6" or "Anti-BSF-2" or "Anti-MGI-2" or "Anti-IL-6" or "Anti-Interleukin-1" or "Anti-Interleukin 1" or "Anti-Interleukin1" or "Anti-IL-1" or "Anti-IL 1" or "Anti-IL1" or "Anti-IL-1a" or "Anti-IL-1alpha" or "Anti-Interleukin 1alpha" or "Anti-IL-1beta" or "Anti-IL-1b" or "Anti-IL1b" or "Anti-Interleukin 1beta" or "Anti-Interleukin-18" or "Anti-Interleukin 18" or "Anti-IL-18" or "Anti-IL18" or "Anti-IL 18" or "AntiInterleukin-6" or "AntiInterleukin 6" or "AntiIL6" or "AntiIL-6" or "AntiIL 6" or "AntiIL-6" or "AntiInterleukin-1" or "AntiInterleukin 1" or "AntiInterleukin1" or "AntiIL-1" or "AntiIL 1" or "AntiIL1" or "AntiIL1a" or "AntiIL1b" or "AntiInterleukin18" or "AntiIL18" or "Pro-Interleukin-6" or "Pro-Interleukin 6" or "Pro-IL-6" or "Pro-IL 6" or "Pro-IL-6" or "Pro-Interleukin-1" or "Pro-Interleukin 1" or "Pro-IL-1" or "Pro-IL 1" or "Pro-IL1" or "Pro-IL-1alpha" or "Pro-Interleukin 1alpha" or "Pro-IL-1beta" or "Pro-IL-1b" or "Pro-IL1b" or "Pro-Interleukin 1beta" or "Pro-Interleukin-18" or "Pro-Interleukin 18" or "Pro-IL-18" or "Pro-IL18" or "Pro-IL 18" or "ProInterleukin-6" or "ProInterleukin 6" or "ProIL6" or "ProIL-6" or "ProIL 6" or "ProIL-6" or "ProInterleukin-1" or "ProInterleukin 1" or "ProInterleukin1" or "ProIL-1" or "ProIL 1" or "ProIL1" or "ProIL-1alpha" or "ProInterleukin 1alpha" or "ProIL-1beta" or "ProIL1b" or "ProInterleukin 1beta" or "ProInterleukin-18" or "ProInterleukin 18" or "ProInterleukin18" or "ProIL-18" or "ProIL18" or "ProIL 18").ti,ab,kf.	8851

6	Modulation MeSH	cytokine receptor antagonist/ or cytokine receptor agonist/ or immunomodulating agent/ or immunosuppressive agent/	122295
7	Cytokine and Receptor MeSH	interleukin 6/ or interleukin 6 receptor/ or interleukin 6 receptor alpha/ or interleukin 1/ or interleukin 1alpha/ or interleukin 1beta/ or interleukin 1 receptor/ or interleukin 18/ or interleukin 18 receptor/ or interleukin 18 receptor alpha/ or interleukin 18 receptor beta/	497511
8	EMTREE interleukin antibody/inhibitor	interleukin 6 antibody/ or interleukin 1 receptor blocking agent/ or interleukin 6 inhibitor/ or interleukin 1 antibody/ or interleukin 1beta antibody/ or interleukin 18 antibody/	19362
9	String 6 AND 7	(6 and 7) or 8	24421
10	String 4 OR 5 OR 9	4 or 5 or 9	147682
11	String 1 AND 10	1 and 10	3820
12	Animal EMBASE	(exp animal experiment/ OR exp animal model/ OR exp experimental animal/ OR exp transgenic animal/ OR exp male animal/ OR exp female animal/ OR exp juvenile animal/ OR animal/ OR chordata/ OR vertebrate/ OR tetrapod/ OR exp fish/ OR amniote/ OR exp amphibia/ OR mammal/ OR exp reptile/ OR exp sauropsid/ OR therian/ OR exp monotreme/ OR placental mammal/ OR exp marsupial/ OR Euarchontoglires/ OR exp Afrotheria/ OR exp Boreoeutheria/ OR exp Laurasiatheria/ OR exp Xenarthra/ OR primate/ OR exp Dermoptera/ OR exp Glires/ OR exp Scandentia/ OR Haplorhini/ OR exp prosimian/ OR simian/ OR exp tarsiiform/ OR Catarrhini/ OR exp Platyrrhini/ OR ape/ OR exp Cercopithecidae/ OR hominid/ OR exp hylobatidae/ OR exp chimpanzee/ OR exp gorilla/ OR exp orang utan/ OR exp cephalopod/) OR (rat OR rats OR animal OR animals OR mice OR "in vivo" OR mouse OR rabbit OR rabbits OR murine OR pig OR pigs OR dog OR dogs OR bovine OR fish OR vertebrate OR vertebrates OR cat OR cats OR rodent OR rodents OR mammal OR mammals OR chicken OR chickens OR monkey OR monkeys OR sheep OR canine OR canines OR porcine OR cattle OR bird OR birds OR hamster OR hamsters OR primate OR primates OR cow OR cows OR chick OR horse OR horses OR avian OR avians OR calf OR swine OR swines OR xenopus OR turkeys OR bear OR bears OR frog OR frogs OR zebrafish OR goat OR goats OR equine OR calves OR poultry OR macaque OR macaques OR mole OR moles OR ovine OR lamb OR lambs OR fishes OR diptera OR amphibian OR amphibians OR snake OR snakes OR ruminant OR ruminants OR hen OR hens OR piglet OR piglets OR feline OR felines OR simian OR simians OR laevis OR trout OR trouts OR teleost OR teleosts OR salmon OR salmons OR seal OR seals OR bull OR bulls OR ewe OR ewes OR hedgehog OR hedgehogs OR macaca OR macacas OR proteus OR pigeon OR pigeons OR bat OR bats OR duck OR ducks OR chimpanzee OR chimpanzees OR baboon OR baboons OR deer OR deers OR rana OR ranas OR carp OR carps OR heifer OR swallow OR swallows OR lizard OR lizards OR canis OR sow OR sows OR cynomolgus OR quail OR quails OR reptile OR reptiles OR turtle OR turtles OR buffalo OR gerbil OR gerbils OR boar OR boars OR squirrel OR squirrels OR oncorhynchus OR mus OR toad OR toads OR fowl OR fowls OR rerio OR danio OR ara OR aras OR musculus OR tadpole OR tadpoles OR mulatta OR salmo OR ram OR eagle OR eagles OR ferret OR ferrets OR	8803426

		goldfish OR catfish OR whale OR whales OR fox OR foxes OR ape OR apes OR elephant OR elephants OR bos OR marmoset OR marmosets OR cod OR cods OR shark OR sharks OR wolf OR eel OR eels OR auratus OR rattus OR zebra OR zebras OR tilapia OR tilapias OR gilt OR camel OR camels OR squid OR gallus OR marsupial OR marsupials OR vole OR voles OR fascicularis OR ovis OR salmonid OR salmonids OR tiger OR tigers OR dolphin OR dolphins OR robin OR robins OR carpio OR opossum OR opossums OR cyprinus OR salamander OR salamanders OR felis OR mink OR minks OR swan OR swans OR norvegicus OR bufo OR torpedo OR bass OR lamprey OR lampreys OR sus OR python OR pythons OR tetrapod OR tetrapods OR shrew OR shrews OR lion OR lions OR hog OR hogs OR songbird OR songbirds OR oreochromis OR starling OR starlings OR caprine OR carassius OR owl OR owls OR newt OR newts OR papio OR scrofa OR hare OR hares OR gorilla OR gorillas OR flounder OR flounders OR goose OR herring OR herrings OR therian OR buffaloes OR canary OR sparrow OR sparrows OR microtus OR octopus OR troglodytes OR tuna OR amphibia OR chinchilla OR chinchillas OR ide OR oryzias OR cervus OR kangaroo OR kangaroos OR armadillo OR armadillos OR callithrix OR "pan troglodytes" OR saimiri OR cichlid OR cichlids OR donkey OR donkeys OR bream OR char OR chars OR finch OR raccoon OR raccoons OR bothrops OR anguilla OR perch OR cricetus OR seabird OR seabirds OR buck OR bucks OR naja OR coturnix OR salmonids OR geese OR minnow OR minnows OR raptor OR raptors OR merione OR meriones OR rodentia OR elaphus OR amniote OR amniotes OR elasmobranch OR emu OR emus OR peromyscus OR hominid OR hominids OR bubalus OR crotalus OR gull OR gulls OR anas OR anura OR lemur OR lemurs OR crow OR crows OR camelus OR gibbon OR gibbons OR waterfowl OR parrot OR parrots OR eels OR cob OR stickleback OR sticklebacks OR columba OR mesocricetus OR ambystoma OR raven OR ravens OR gadus OR penguin OR penguins OR orangutan OR orangutans OR sturgeon OR sturgeons OR cuniculus OR aves OR virginianus OR cephalopod OR cephalopods OR cebus OR sparus OR tortoise OR tortoises OR guttata OR morhua OR unguiculatus OR dogfish OR vulpes OR mallard OR mallards OR apodemus OR alligator OR alligators OR oryctolagus OR llama OR llamas OR reindeer OR mustela OR duckling OR ducklings OR wolves OR sander OR amazona OR zebu OR badger OR badgers OR dove OR doves OR ictalurus OR capra OR capras OR equus OR camelid OR camelids OR poecilia OR mule OR mules OR perciformes OR salvelinus OR labrax OR cyprinidae OR ariidae OR crocodile OR crocodiles OR fundulus OR dicentrarchus OR clarias OR cercopithecus OR chiroptera OR alpaca OR alpacas OR pike OR pikes OR paralichthys OR puma OR pumas OR didelphis OR pisces OR macropus OR triturus OR bison OR bisons OR epinephelus OR gasterosteus OR panthera OR acipenser OR mackerel OR mackerels OR tamarin OR tamarins OR ostrich OR anolis OR vervet OR vervets OR wallaby OR glareolus OR beaver OR beavers OR dromedary OR catus OR killifish OR pimephales OR promelas OR aotus OR phoca OR panda OR pandas OR porpoise OR porpoises OR myotis OR yak OR yaks OR agkistrodon OR vipera OR otter OR otters OR turbot OR turbots OR squamate OR carnivora OR mullet OR mullets OR hawk OR hawks OR taeniopygia OR seahorse OR seahorses OR "poecilia reticulata" OR falcon OR falcons OR prosimian OR prosimians OR parus OR perca OR fingerling OR fingerlings OR antelope OR antelopes OR tupaia OR passeriformes OR sepia OR saguinus OR coyote OR coyotes OR pongo OR meleagris OR reptilia OR lepus	

		OR psittacine OR hagfish OR warbler OR warblers OR "russell s viper" OR "russell s vipers" OR smolt OR smolts OR budgerigar OR sardine OR sardines OR cavia OR cavias OR hyla OR pleurodeles OR siluriformes OR "great tit" OR "great tits" OR guppy OR bonobo OR bonobos OR rutilus OR trichosurus OR muridae OR phodopus OR channa OR squalus OR lynx OR sturnus OR petromyzon OR vitulina OR monodelphis OR cuttlefish OR adder OR adders OR lepomis OR canaria OR gambusia OR guppies OR xiphophorus OR flatfish OR koala OR koalas OR labeo OR stingray OR stingrays OR chelonia OR lampetra OR spermophilus OR crocodilian OR "passer domesticus" OR sciurus OR artiodactyla OR ranidae OR corvus OR necturus OR platypus OR canaries OR bovid OR lagopus OR trimeresurus OR gariepinus OR marten OR martens OR drosophilidae OR mugil OR sunfish OR porcellus OR cypriniformes OR alouatta OR scophthalmus OR anser OR electrophorus OR putorius OR iguana OR iguanas OR lama OR lamas OR takifugu OR circus OR eptesicus OR flycatcher OR galago OR galagos OR trachemys OR lungfish OR characiformes OR shorebird OR shorebirds OR giraffe OR giraffes OR micropterus OR scyliorhinus OR cichlidae OR loligo OR porcupine OR porcupines OR chub OR chubs OR solea OR pleuronectes OR hylidae OR viperidae OR echis OR sorex OR anchovy OR lagomorph OR ostriches OR vulture OR vultures OR whitefish OR araneus OR jird OR jirds OR tern OR esox OR drake OR drakes OR elapidae OR gallopavo OR chordata OR myodes OR caretta OR serinus OR grouse OR misgurnus OR meles OR blackbird OR blackbirds OR coregonus OR bobwhite OR bobwhites OR heteropneustes OR mammoth OR mammoths OR turdus OR rhinella OR ateles OR characidae OR clupea OR bungarus OR brill OR "struthio camelus" OR sloth OR sloths OR pteropus OR sculpin OR anthropoids OR pollock OR pollocks OR morone OR "pan paniscus" OR litoria OR chipmunk OR chipmunks OR balaenoptera OR marmota OR melopsittacus OR hyrax OR lemming OR lemmings OR halibut OR hylobates OR lates OR caiman OR caimans OR sigmodon OR stenella OR barbel OR barbels OR sterna OR parakeet OR parakeets OR phocoena OR leptodactylus OR canidae OR buteo OR harengus OR gopher OR gophers OR marmot OR marmots OR gosling OR goslings OR platichthys OR gar OR gars OR sebastes OR marsupialia OR notophthalmus OR gazelle OR gazelles OR	

		insectivora OR paridae OR felidae OR russula OR galliformes OR bombina OR colobus OR echidna OR echidnas OR seabass OR syncerus OR plaice OR "blue tit" OR "blue tits" OR pagrus OR catfishes OR cetacea OR barbus OR cygnus OR ficedula OR chamois OR colubridae OR perches OR coelacanth OR fitch OR urodela OR cynops OR martes OR halichoerus OR aix OR salmonidae OR leuciscus OR magpie OR magpies OR silurus OR whiting OR whitings OR anseriformes OR colinus OR rhea OR chlorocebus OR octodon OR acinonyx OR mouflon OR mouflons OR ibex OR tetraodon OR bufonidae OR equidae OR jackal OR cephalopoda OR dendroaspis OR glama OR muskrat OR muskrats OR sable OR sables OR wildebeest OR streptopelia OR albifrons OR vespertilionidae OR woodpecker OR woodpeckers OR muntjac OR muntjacs OR archosaur OR branta OR cricetulus OR megalobrama OR poeciliidae OR desmodus OR snakehead OR snakeheads OR tench OR teal OR teals OR bandicoot OR bandicoots OR apteronotus OR phyllostomidae OR crocidura OR buzzard OR buzzards OR larimichthys OR cercocebus OR pipistrellus OR erithacus OR impala OR impalas OR rousettus OR haddock OR haddocks OR tinca OR ratite OR calidris OR cynoglossus OR hypophthalmichthys OR bullock OR bullocks OR dromedaries OR alectoris OR filly OR salamandra OR cingulata OR bitis OR grus OR ammodytes OR macaw OR macaws OR hypoleuca OR sapajus OR cyprinodontiformes OR hippopotamus OR pelophylax OR capybara OR capybaras OR weasel OR weasels OR cairina OR cynomys OR lutra OR cockatoo OR cockatoos OR lachesis OR lagomorpha OR rupicapra OR daboia OR "orang utan" OR "orang utans" OR platyrrhini OR charadriiformes OR micrurus OR psittaciformes OR spalax OR loris OR mustelidae OR sylvilagus OR vitticeps OR cockatiel OR mustelus OR cottus OR erythrocebus OR dipodomys OR platessa OR callicebus OR loricariidae OR catostomus OR cuneata OR cyanistes OR cyprinodon OR sigmodontinae OR elasmobranchii OR trichechus OR sauropsid OR xenarthra OR dormouse OR perissodactyla OR nautilus OR cirrhinus OR gulo OR gulos OR tragelaphus OR merula OR numida OR sciaenidae OR cerastes OR sciuridae OR gibbosus OR octopuses OR eland OR elands OR phyllomedusa OR pogona OR walrus OR agamidae OR leptodactylidae OR ridibundus OR leontopithecus OR anteater OR anteaters OR pelodiscus OR cebidae OR columbianus OR "pelteobagrus fulvidraco" OR hominoidea OR mandrillus OR "zonotrichia leucophrys" OR agama OR gobiocypris OR "bearded dragon" OR "bearded dragons" OR sarotherodon OR talpa OR discoglossus OR hagfishes OR sphenodon OR gudgeon OR amphiuma OR aythya OR tenrec OR tenrec OR hominidae OR risoria OR salamandridae OR camelidae OR columbiformes OR latimeria OR plover OR plovers OR afrotheria OR "falco sparverius" OR polecat OR polecats OR crotalinae OR salvadora OR tarsier OR lucioperca OR anchovies OR lungfishes OR terrapin OR "dromaius novaehollandiae" OR lateolabrax OR eigenmannia OR pelamis OR theropithecus OR murinae OR gander OR gymnotus OR pseudacris OR gymnophiona OR gymnotiformes OR laticauda OR falconiformes OR dugong OR dugongs OR pintail OR pintails OR rook OR rooks OR lasiurus OR catshark OR catsharks OR micropogonias OR "red junglefowl" OR paddlefish OR ophiophagus OR hollandicus OR nymphicus OR pimelodidae OR aepyceros OR cobitidae OR strigiformes OR cobitis OR dormice OR alytes OR calloselasma OR guanaco OR guanacos OR phasianidae OR "round goby" OR trichogaster OR catarrhini OR eelpout OR eelpouts OR galaxias OR gaur OR pungitius OR suslik OR susliks OR flatfishes OR percidae OR caprinae OR	

todarodes OR osmerus OR ameiurus OR anthropoidea OR "castor canadensis" OR pouting OR poutings OR tetraodontiformes OR arvicolinae OR siamang OR siamangs OR "castor fiber" OR nomascus OR "red knot" OR "red knots" OR syngnathidae OR iguanidae OR eretmochelys OR ursidae OR callimico OR columbidae OR microhylidae OR anaxyrus OR menidia OR pipistrelle OR greylag OR pipidae OR scandentia OR bowfin OR bowfins OR dendrobatidae OR zenaida OR bushbaby OR harrier OR harriers OR macropodidae OR pygerythrus OR clupeidae OR odorrana OR corvidae OR jerboa OR jerboas OR canutus OR hylobatidae OR clupeiformes OR "great cormorant" OR "great cormorants" OR scorpaeniformes OR chondrostean OR garfish OR proboscidea OR psetta OR diapsid OR serotinus OR tetrao OR walruses OR carcharhiniformes OR leucoraja OR pumpkinseed OR dosidicus OR acipenseriformes OR daubentonii OR emberizidae OR gadiformes OR hyraxes OR stizostedion OR wolverine OR wolverines OR lissotriton OR acanthurus OR centrarchidae OR gloydius OR

laurasiatheria OR limosa OR psittacula OR leporidae OR proteidae OR zander OR zanders OR arapaima OR bagridae OR cyprinodontidae OR mithun OR pandion OR jackdaw OR jackdaws OR procyonidae OR carus OR jaculus OR salmoniformes OR "common sole" OR "common soles" OR protobothrops OR calamita OR brachyteles OR trionyx OR turdidae OR boidae OR luscinia OR pugnax OR euarchontoglires OR saithe OR saithes OR symphalangus OR aardvark OR aardvarks OR oystercatcher OR oystercatchers OR arius OR corydoras OR poacher OR poachers OR aurochs OR cebuella OR crecca OR lemuridae OR sirenia OR lemmus OR perdix OR glires OR lepidosaur OR muskox OR deinagkistrodon OR pholidota OR holocephali OR cercopithecinae OR clariidae OR agapornis OR doryteuthis OR tyrannidae OR dicroglossidae OR godwit OR godwits OR monedula OR pongidae OR atheriniformes OR colobinae OR lophocebus OR atelidae OR cottidae OR leucopsis OR acanthuridae OR didelphimorphia OR elver OR elvers OR lapponica OR dermoptera OR "european hake" OR "european hakes" OR gerbillinae OR banteng OR hartebeest OR hartebeests OR hogget OR haematopus OR "anguis fragilis" OR "grey heron" OR "grey herons" OR "blue whiting" OR "blue whitings" OR furnariidae OR macrovipera OR esocidae OR lapwing OR lapwings OR mylopharyngodon OR wallabia OR beloniformes OR potoroo OR potoroos OR "athene noctua" OR pleuronectidae OR bushbabies OR muscicapidae OR alligatoridae OR fuligula OR "bush baby" OR guineafowl OR spoonbill OR spoonbills OR viverridae OR catostomidae OR zebrafishes OR ibexes OR vendace OR estrildidae OR monotremata OR sepiella OR ambystomatidae OR shelduck OR shelducks OR treeshrew OR treeshrews OR hoplobatrachus OR pochard OR hoolock OR hoolocks OR lynxes OR antilope OR antilopes OR blackbuck OR blackbucks OR cricetinae OR paramisgurnus OR skylark OR

	skylarks OR soleidae OR allobates OR "northern wheatear" OR "northern wheatears" OR pitheciidae OR takin OR theria OR vanellus OR galaxiidae OR lorisidae OR ostralegus OR palaeognathae OR "stone loach" OR alauda OR callitrichinae OR caniformia OR duttaphrynus OR ictaluridae OR osteoglossiformes OR poultries OR curema OR "ruddy turnstone" OR "ruddy turnstones" OR sheatfish OR sunfishes OR centropomidae OR hemachatus OR platalea OR thamnophilidae OR "song thrush" OR atherinopsidae OR siluridae OR tadorna OR chroicocephalus OR ermine OR ermines OR gavialis OR ruff OR tupaiidae OR diprotodontia OR hyaenidae OR antilopinae OR crocodylidae OR herpestidae OR hippopotamidae OR "northern shoveler" OR "round gobies" OR cheirogaleidae OR indriidae OR fundulidae OR pythonidae OR rhynchocephalia OR anodorhynchus OR "red-backed shrike" OR "red-backed shrikes" OR triakidae OR phalangeridae OR aoudad OR boreoeutheria OR "eurasian jay" OR "eurasian jays" OR feliformia OR haplorhini OR osteoglossidae OR paenungulata OR struthioniformes OR ferina OR sanderling OR sanderlings OR spheniscidae OR cuttlefishes OR cygnet OR dasycneme OR gadwall OR gadwalls OR "pelobates fuscus" OR wryneck OR wrynecks OR afrosoricida OR culaea OR "dover sole" OR "dover soles" OR paralichthyidae OR passeridae OR osteolaemus OR "song thrushes" OR bluethroat OR bluethroats OR hydrophiidae OR megrim OR mephitidae OR strepsirhini OR tomistoma OR epidalea OR osmeriformes OR "bush babies" OR tarsiiform OR atelinae OR bufotes OR "eurasian coot" OR "eurasian coots" OR galagidae OR geopelia OR philomachus OR tubulidentata OR bombinatoridae OR pelobatidae OR tachysurus OR ailuridae OR woodlark OR woodlarks OR alcelaphinae OR redshank OR redshanks OR salientia OR "sand smelt" OR "sand smelts" OR woodmice OR woodmouse OR dasyproctidae OR "eurasian wigeon" OR "eurasian wigeons" OR garganey OR garganeys OR "lemon sole" OR "lemon soles" OR "common dab" OR "common dabs" OR graylag OR graylags OR leucorodia OR osphronemidae OR bewickii OR "common moorhen" OR "common moorhens" OR decapodiformes OR gobbler OR gobblers OR odontophoridae OR paddlefishes OR eutheria OR salmonine OR esociformes OR "eurasian woodcock" OR "eurasian woodcocks" OR "european smelt" OR "european smelts" OR goldfishes OR tenches OR tyranni OR "common chaffinch" OR "common chaffinchs" OR "common redstart" OR "common redstarts" OR "common roach" OR "common roachs" OR "great knot" OR "great knots" OR potoroidae OR alytidae OR coregonine OR dipteral OR leveret OR "poeciliopsis gracilis" OR amphiumidae OR batrachoidiformes OR "bighead goby" OR heteropneustidae OR lullula OR "norway pout" OR "norway pouts" OR sipunculida OR dogfishes OR sebastidae OR tarsiidae OR alethinophidia OR "common nase" OR "common nases" OR "common sandpiper" OR "common sandpipers" OR "eurasian blackcap" OR "eurasian blackcaps" OR pterocnemia OR syngnathiformes OR "common chaffinches" OR eupleridae OR octopodiformes OR phascolarctidae OR scophthalmidae OR "starry smooth-hound" OR "starry smooth-hounds" OR whitefishes OR cuniculidae OR "european sprat" OR "european sprats" OR "rosy bitterling" OR "rosy bitterlings" OR "common dace" OR "common daces" OR "lesser weever" OR "lesser weevers" OR scaldfish OR "water rail" OR "water rails" OR alouattinae OR centrarchiformes OR "common whitethroat" OR "common whitethroats" OR gavialidae OR "grey gurnard" OR "grey gurnards" OR lateolabracidae OR rheiformes OR "tub gurnard" OR "tub gurnards" OR "common chiffchaff" OR "common chiffchaffs"	

		OR garfishes OR "lesser whitethroat" OR "lesser whitethroats" OR myoxidae OR seabasses OR spariformes OR umbridae OR "yellow boxfish" OR anabantiformes OR aotidae OR "common bleak" OR "common bleaks" OR "common rudd" OR "common rudds" OR "greater pipefish" OR hapale OR nandiniidae OR "stone loaches" OR whinchat OR whinchats OR acanthuriformes OR "brotula barbata" OR "common ling" OR "common lings" OR "common roaches" OR cottonrat OR cottonrats OR douroucoulis OR dromaiidae OR fitches OR fitchew OR galaxiiformes OR laprine OR saimiriinae OR solenette OR tarsii OR "tompot blenny" OR "common dragonet" OR "common dragonets" OR "longspined bullhead" OR "longspined bullheads" OR monotremate OR monotremates OR pempheriformes OR perdicinae OR presbytini OR smegmamorpha OR "bighead gobies" OR "carangaria incertae sedis" OR coiidae OR "fivebeard rockling" OR foulmart OR foumart OR grasskeet OR "greater pipefishes" OR ibices OR millionfish OR muguliformes OR "norwegian topknot" OR peewit OR "red sea sailfin tang" OR rupicapras OR sheatfishes OR "tompot blennies" OR "twait shad" OR "yellow boxfishes").ti,ab,kw.	
13	String 11 AND 12	11 and 12	**1570**

Supplementary Table 3. Actions taken to acquire missing/unclear outcome data. SD = standard deviation. SEM = standard error of the mean. N = number of animals.

Missing/unclear outcome data	**Contact author**	**Response**	**Action**
	SD/SEM/Mean		
Not stated whether the outcome is displayed as the mean.	The separate points could not be measured, the authors were contacted. (Tian et al., 2020; Wang et al., 2020)	No	It was assumed to be the mean.
	No (Dragoljevic et al., 2020; Jia et al., 2023)	x	The separate data points were measured to determine whether the presented value is the mean and used this value.
Not clear whether it is the SD or SEM.	No (Dragoljevic et al., 2020; Jia et al., 2023)	x	The separate data points were measured to determine whether the presented value is the SD or SEM and use the presented value.

	The separate points could not be measured, the authors of the paper were contacted. (Tian et al., 2020; Wang et al., 2020)	No	Assumed to be the SEM.
SEM nor SD are presented.	No (Bhaskar et al., 2011; Fuster et al., 2017)	x	The separate points were measured, and the mean and SD were calculated, which were used for analysis.
	The separate data points cannot be measured. Authors were contacted. (Schuett et al., 2012)	Yes, received the data and used those.	x
SEM nor SD nor mean are presented.	The separate data points cannot be measured. Authors were contacted. (Abderrazak et al., 2015)	No	The paper was excluded for MA.
Boxplot	No (Orecchioni et al., 2022)	x	The separate data points were measured and the mean and SD were calculated and used.
	N-values		
N is not presented.	No	x	The N was counted. (Christersdottir et al., 2019; Dragoljevic et al., 2020; Fuster et al., 2017; Jin et al., 2022; Orecchioni et al., 2022)
	No	x	Used the N-values from tables with the separate data points. (Fidler et al., 2021)
	Authors were contacted. (Meng et al., 2016)	No	Counting is difficult, use the counted N.
N is not clear.	N cannot be counted. Authors were contacted. (Wen et al., 2021)	No	Took the only presented N.
	No (Yalcinkaya et al., 2023)	x	Counted N.
N is presented as a range.	No (Denes et al., 2012; Dragoljevic et al., 2020; Hettwer et al., 2022; Orecchioni et al., 2022; Schwarz et al., 2023; Tenger et al., 2005; Wu et al., 2022)	x	The individual data points were counted.
	No (Vromman et al., 2019)	x	The N cannot be counted, choose the lowest value.
	The n cannot be counted, authors were contacted. (P. Luo et al., 2020)	No	The lowest potential value was used.
N is presented as a range and difficult to count properly. Or the n-values are switched for the groups in the methods compared to the graph and the legend says something different.	The authors were contacted. (Schuett et al., 2012)	Yes, received the data and used those.	x
N is presented as ≥.	No (Jin et al., 2022)	x	N was counted.
N in figure legend is different from N in tables with the separate data points.	No (Fidler et al., 2021)	x	Used the N-values from tables with the separate data points.
N is different in graph compared to legend.	No (Traughber et al., 2023)	x	Counted N.

N different in graph compared to N in Materials and Methods.	No (Whitman et al., 2002)	x	Counted N.
	Other		
Same data presented in two papers.(Bhat et al., 2015, 2018)	No	x	One paper was excluded for meta-analysis. (Bhat et al., 2015)
Data presented in graphs, but separate data points also presented in tables.	No (Fidler et al., 2021)	x	Used the separate data points from tables to calculate the mean and SD and used those.

Supplementary Table 4. Study characteristics of the included records in the systematic review. Columns divided over left and right pages.

Paper information						Animal model						
Author	Year of publication	Title	Journal	Language	doi	Species	Strain	Genetic background	Type of atherosclerotic model	Sex	Age (at disease induction), t=0	Disease induction method
Abderrazak	2015	Anti-Inflammatory and Antiatherogenic Effects of the NLRP3 Inflammasome Inhibitor Arglabin in ApoE2.Ki Mice Fed a High-Fat Diet	Circulation	English	10.1161/CIRCULATIONAHA.114.013730.	Mice	ApoE2.Ki	C57BL/6	aortic sinus AND whole aorta	f	6 weeks	Diet
Akita, K	2017	An Interleukin-6 Receptor Antibody Suppresses Atherosclerosis in Atherogenic Mice	Frontiers in Cardiovascular Medicine	English	10.3389/fcvm.2017.00084	Mice	$LDLr^{-/-}$	_	Aortic root AND aortas (en face)	_	_	Diet
Akita, K	2017	An Interleukin-6 Receptor Antibody Suppresses Atherosclerosis in Atherogenic Mice	Frontiers in Cardiovascular Medicine	English	10.3389/fcvm.2017.00084	Mice	$IkBNS^{-/-}/LDLr^{-/-}$	_	Aortic root AND aortas (en face)	_	_	Diet
Bhaskar	2011	Monoclonal antibodies targeting IL-1 beta reduce biomarkers of atherosclerosis in vitro and inhibit atherosclerotic plaque formation in Apolipoprotein E-deficient mice	Atherosclerosis	English	10.1016/j.atherosclerosis.2011.02.026	Mice	$ApoE^{-/-}$	C57BL/6	aorta en face AND brachiocephalic arteries	m	6 weeks	Diet
Bhaskar	2011	Monoclonal antibodies targeting IL-1 beta reduce biomarkers of atherosclerosis in vitro and inhibit atherosclerotic plaque formation in Apolipoprotein E-deficient mice	Atherosclerosis	English	10.1016/j.atherosclerosis.2011.02.026	Mice	$ApoE^{-/-}$	C57BL/6	aorta en face AND brachiocephalic arteries	m	6 weeks	Diet
Bhaskar	2011	Monoclonal antibodies targeting IL-1 beta reduce biomarkers of atherosclerosis in vitro and inhibit atherosclerotic plaque formation in Apolipoprotein E-deficient mice	Atherosclerosis	English	10.1016/j.atherosclerosis.2011.02.026	Mice	$ApoE^{-/-}$	C57BL/6	aorta en face AND brachiocephalic arteries	m	6 weeks	Diet
Bhat	2015	Interleukin-18-induced atherosclerosis involves CD36 and NF-kB crosstalk in Apo E-/- mice	Journal of Cardiology	English	10.1016/j.jjcc.2014.10.012	Mice	$ApoE^{-/-}$	C57BL/6	ascending aorta	m	12 weeks when intervention starts. No disease induction	_
Bhat	2018	Terminalia arjuna prevents Interleukin-18-induced atherosclerosis via modulation of NF-jB/PPAR-c-mediated pathway in Apo E-/ - mice	Inflammopharmacol	English	10.1007/s10787-017-0357-9	Mice	$ApoE^{-/-}$	C57BL/6	ascending aorta	m	12 weeks when intervention starts. No disease induction	_
Chen	2012	Marked Acceleration of Atherosclerosis After Lactobacillus casei–Induced Coronary Arteritis in a Mouse Model of Kawasaki Disease	Arterioscler Thromb Vasc Biol.	English	10.1161/ATVBAHA.112.249417.	Mice	$ApoE^{-/-}$	C57BL/6	aortic sinus AND aortic arch and aorta en face	m	7 weeks	diet
Chen, J	2022	Interleukin 6-regulated macrophage polarization controls atherosclerosisassociated vascular intimal hyperplasia	Front. Immunol.	English	10.3389/fimmu.2022.952164	Mice	$ApoE^{-/-}$	_	femoral artery	m AND f	12 weeks	diet
Christersdottir	2019	Prevention ofradiotherapy-induced arterial inflammation by interleukin-1 blockade	European Heart Journal	English	10.1093/eurheartj/ehz206	Mice	$ApoE^{-/-}$	C57BL/6	aortic root AND aortic arch en face and aortic innominate artery	f	9 to 10 weeks when intervention starts. No disease induction	_
Christersdottir	2019	Prevention ofradiotherapy-induced arterial inflammation by interleukin-1 blockade	European Heart Journal	English	10.1093/eurheartj/ehz206	Mice	$ApoE^{-/-}$	C57BL/6	aortic root AND aortic arch en face and aortic innominate artery	f	9 to 10 weeks when intervention starts. No disease induction	_
de Nooijer	2004	Overexpression of IL-18 Decreases Intimal Collagen Content and Promotes a Vulnerable Plaque Phenotype in Apolipoprotein-E–Deficient Mice	Arterioscler Thromb Vasc Biol.	English	10.1161/01.ATV.0000147126.99529.0a	Mice	$ApoE^{-/-}$	_	carotid	f	10 to 12 weeks	perivascular collar placement
Denes	2012	Interleukin-1 Mediates Neuroinflammatory Changes Associated With Diet-Induced Atherosclerosis	J AmHeart Assoc.	English	10.1161/JAHA.112.002006.	Mice	$ApoE^{-/-}$	_	aortic root AND whole aorta en face	m	10 weeks	Diet
Denes	2012	Interleukin-1 Mediates Neuroinflammatory Changes Associated With Diet-Induced Atherosclerosis	J AmHeart Assoc.	English	10.1161/JAHA.112.002006.	Mice	$ApoE^{-/-}$	_	aortic root AND whole aorta en face	m	10 weeks	Diet
Dragoljevic	2020	Inhibition of interleukin-1b signalling promotes atherosclerotic lesion remodelling in mice with inflammatory arthritis	Clinical & Translational Immunology	English	10.1002/cti2.1206	Mice	$Ldlr^{-/-}$	C57BL/6	aortic sinus AND aortic arch en face	f	_	Diet
Elhage	1998	Differential Effects of Interleukin-1 Receptor Antagonist and Tumor Necrosis Factor Binding Protein on Fatty-Streak Formation in Apolipoprotein E–Deficient Mice	Circulation	English	?	Mice	$ApoE^{-/-}$	C57BL/6	aortic sinus	f	2 months	Atherogenic diet and E2 pellets
Elhage	1998	Differential Effects of Interleukin-1 Receptor Antagonist and Tumor Necrosis Factor Binding Protein on Fatty-Streak Formation in Apolipoprotein E–Deficient Mice	Circulation	English	?	Mice	$ApoE^{-/-}$	C57BL/6	aortic sinus	m	2 months	Atherogenic diet and E2 pellets
Fidler	2021	The AIM2 inflammasome exacerbates atherosclerosis in clonal haematopoiesis	Nature	English	10.1038/s41586-021-03341-5.	Mice	$Ldlr^{-/-}$ mice with 100% littermate control (contained either an ellele with Cre or the Jak2vf transgene, not both) bone marrow	C57BL/6	aortic root	f	12-16 week	Diet
Fidler	2021	The AIM2 inflammasome exacerbates atherosclerosis in clonal haematopoiesis	Nature	English	10.1038/s41586-021-03341-5.	Mice	$Ldlr^{-/-}$ mice with 100% Jak2VF bone marrow	C57BL/6	aortic root	f	12-16 week	Diet
Fidler	2021	The AIM2 inflammasome exacerbates atherosclerosis in clonal haematopoiesis	Nature	English	10.1038/s41586-021-03341-5.	Mice	$Ldlr^{-/-}$ mice with 100% Jak2VF bone marrow	C57BL/6	aortic root	f	12-16 week	Diet
Freigang, S	2011	Nrf2 is essential for cholesterol crystal-induced inflammasome activation and exacerbation of atherosclerosis	Eur. J. Immunol.	English	10.1002/eji.201041316	Mice	$Nrf2^{+/}Apoe^{-/-}$	C57BL/6	En face aortae	_	_	Diet
Freigang, S	2011	Nrf2 is essential for cholesterol crystal-induced inflammasome activation and exacerbation of atherosclerosis	Eur. J. Immunol.	English	10.1002/eji.201041316	Mice	$Nrf2^{-/-}Apoe^{-/-}$	C57BL/6	En face aortae	_	_	Diet
Fukumoto	1997	Inflammatory Cytokines Cause Coronary Arteriosclerosis-Like Changes and Alterations in the Smooth-Muscle Phenotypes in Pigs	Journal of Cardiovascular Pharmacology	English	?	Pigs	_	_	Coronary artery	m	2-3 months old	dissected segments of the coronary arteries were gently wrapped with cotton mesh and sepharose beads suspension
Fuster	2017	Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice	Science	English	10.1126/science.aag1381.	Mice	$Ldlr^{-/-}$, 10% CD45.2+Tet2+/+ 90% CD45.1+Tet2+/+ BM cells	C57BL/6	aortic root	f	_	Diet
Fuster	2017	Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice	Science	English	10.1126/science.aag1381.	Mice	$Ldlr^{-/-}$, 10% CD45.2+Tet2-/- 90% CD45.1+Tet2+/+ BM cells	C57BL/6	aortic root	f	_	Diet
Gomez	2018	Interleukin-1β has atheroprotective effects in advanced atherosclerotic lesions of mice	Nat Med.	English	10.1038/s41591-018-0124-5	Mice	$ApoE^{-}$ Myh11 ERT2 Cre YFP	_	whole aorta AND BCAssections	m	8 weeks	Diet
Hettwer, J	2022	Interleukin-1b suppression dampens inflammatory leucocyte production and uptake in atherosclerosis	Cardiovascular Research	English	10.1093/cvr/cvab337	Mice	$ApoE^{-/-}$	C57BL/6J	aortic root	m AND f	8- to 12 weeks	Diet
Hettwer, J	2022	Interleukin-1b suppression dampens inflammatory leucocyte production and uptake in atherosclerosis	Cardiovascular Research	English	10.1093/cvr/cvab337	Mice	$ApoE^{-/-}$	C57BL/6J	aortic root	m AND f	8- to 12 weeks	Diet for 2 weeks and then permanent coronary artery ligation. Continued diet for another 8 weeks
Hohensinner	2021	Pharmacological inhibition of fatty acid oxidation reduces atherosclerosis progression by suppression of macrophage NLRP3 inflammasome activation	Biochemical Pharmacology	English	10.1016/j.bcp.2021.114634	Mice	$Ldlr^{-/-}$	C57BL/6	whole aorta en face	m	12 weeks	Diet
Imai	2011	Proatherogenic Effect of Interleukin-18 is Exerted with High-fat Diet, but not with Normal Diet in Spontaneously Hyperlipidemic Mice	Journal of Atherosclerosis and Thrombosis	English	_	Mice	Spontaneously hyperlipidemic (SHL)	C57BL/6	aortic root	m	diet starts at 10 weeks	Spontaneously hyperlipidemic
Imai	2011	Proatherogenic Effect of Interleukin-18 is Exerted with High-fat Diet, but not with Normal Diet in Spontaneously Hyperlipidemic Mice	Journal of Atherosclerosis and Thrombosis	English	_	Mice	Spontaneously hyperlipidemic (SHL)	C57BL/6	aortic root	m	diet starts at 10 weeks	Spontaneously hyperlipidemic
Janssen, H	2015	Acute perioperative-stress-induced increase of atherosclerotic plaque volume and vulnerability to rupture in apolipoprotein-Edeficient mice is amenable to statin treatment and IL-6 inhibition	Disease Models & Mechanisms	English	10.1242/dmm.018713	Mice	$ApoE^{-/-}$	C57BL6/J	innominate artery	m AND f	8 weeks of age start diet	7 weeks of diet and then a double-hit perioperative stress model
Janssen, H	2015	Acute perioperative-stress-induced increase of atherosclerotic plaque volume and vulnerability to rupture in apolipoprotein-Edeficient mice is amenable to statin treatment and IL-6 inhibition	Disease Models & Mechanisms	English	10.1242/dmm.018713	Mice	$ApoE^{-/-}$	C57BL6/J	innominate artery	m AND f	8 weeks of age start diet	7 weeks of diet and then a double-hit perioperative stress model
Jia	2023	Serum amyloid A and interleukin -1β facilitate LDL transcytosis across endothelial cells and atherosclerosis via NF-κB/caveolin-1/cavin-1 pathway	Atherosclerosis	English	10.1016/j.atherosclerosis.2023.03.004	Mice	$ApoE^{-/-}$	_	aortic root AND Ascending aorta en face	m	~ 15 weeks	Diet
Jin, Y	2022	Novel role for caspase 1 inhibitor VX765 in suppressing NLRP3 inflammasome assembly and atherosclerosis via promoting mitophagy and efferocytosis	Cell Death and Disease	English	10.1038/s41419-022-04966-8	Mice	$Ldlr^{-/-}$	C57BL/6	whole aorta AND aortic root	m AND f	6-8-weeks	Diet
Jin, Y	2022	Novel role for caspase 1 inhibitor VX765 in suppressing NLRP3 inflammasome assembly and atherosclerosis via promoting mitophagy and efferocytosis	Cell Death and Disease	English	10.1038/s41419-022-04966-8	Mice	$ApoE^{-/-}$	C57BL/6	whole aorta AND aortic root	m AND f	6-8-weeks	Diet
Jin, Y	2022	Novel role for caspase 1 inhibitor VX765 in suppressing NLRP3 inflammasome assembly and atherosclerosis via promoting mitophagy and efferocytosis	Cell Death and Disease	English	10.1038/s41419-022-04966-8	Mice	$ApoE^{-/-}$	C57BL/6	whole aorta	m AND f	6-8-weeks	Diet
Jin, Y	2022	Novel role for caspase 1 inhibitor VX765 in suppressing NLRP3 inflammasome assembly and atherosclerosis via promoting mitophagy and efferocytosis	Cell Death and Disease	English	10.1038/s41419-022-04966-8	Mice	$Nlrp3^{-/-};ApoE^{-/-}$	C57BL/6	whole aorta	m AND f	6-8-weeks	Diet
Karnewar	2024	IL-1β Inhibition Partially Negates the Beneficial Effects of Diet-Induced Atherosclerosis Regression in Mice	Arterioscler Thromb Vasc Biol.	English	10.1161/ATVBAHA.124.320800	Mice	$ApoE^{-/-}$	_	whole aorta AND brachiocephalic arteries ((BCAs) were serially cut into 10-μm-thick sections from the aortic arch to the bifurcation of the right subclavian artery.	m	9 to 11 weeks	Diet

	Intervention of interest												
Type of diet	Cytokines	Cytokine receptors	Type of intervention	Type of immunomodulatory component	Immunomodulator inhibitory (inh) or stimulatory (sti)	Direct (dir) or indirect (indir) modulator	Timing intervention (relative to disease induction)	Timing of outcome assessment (relative to intervention)	Duration	Age at outcome assessment (weeks)	Age range category (weeks)	Included in overall analyses	aorta type chosen for MA
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	ip	natural product			0 weeks	13 weeks	13 weeks	19			
atherosclerosis diet	_	IL-6R	ip	antibody	inh	dir	0 weeks	16 weeks	16 weeks	_			aortic root
atherosclerosis diet	_	IL-6R	ip	antibody	inh	dir	0 weeks	16 weeks	16 weeks	_			aortic root
atherosclerosis diet	IL-1B	_	ip	antibody	inh	dir	0 weeks	16 weeks	16 weeks	22	16 t/m 23	x	aorta en face
atherosclerosis diet	IL-1B	_	ip	antibody	inh	dir	0 weeks	16 weeks	16 weeks	22	16 t/m 23	x	aorta en face
atherosclerosis diet	IL-1B	_	ip	antibody	inh	dir	0 weeks	16 weeks	16 weeks	22	16 t/m 23	x	aorta en face
Normal diet	IL-18	_	ip	recombinant mouse interleukin			0	2 months	2 months (treatment group received 1 month il-18 and 1 month PBS)	21			
Normal diet	IL-18	_	ip	recombinant mouse interleukin	sti	dir	0	2 months	2 months (treatment group received 1 month il-18 and 1 month PBS)	21	16 t/m 23	x	ascending aorta
atherosclerosis diet	_	IL-1R	ip	recombinant human antagonist	inh	dir	minus 2 weeks (Day1 - day 5)	10 weeks	7 days	15	t/m 15	x	aortic sinus
atherosclerosis diet	IL-6	_	ip	antibody	inh	dir	0 weeks	3 months	12 weeks	25,5			
Normal diet	_	IL-1R	ip	recombinant human antagonist	inh	dir	0	10 weeks	2 weeks	19 to 20	16 t/m 23	x	aortic root
Normal diet	_	IL-1R	ip	recombinant human antagonist			0	10 weeks	2 weeks	19 to 20			
atherosclerosis diet	IL-18	_	iv	adenovirus			5 weeks	2 weeks	2 weeks	17 to 19			
atherosclerosis diet	IL-1B	_	peripheral	antibody	inh	dir	_	_	_	18	16 t/m 23	x	aortic root
atherosclerosis diet	IL-1B	_	peripheral	antibody	inh	dir	_	_	_	18	16 t/m 23	x	aortic root
atherosclerosis diet followed by normal diet	_	IL-1R	ip	recombinant human antagonist	inh	dir	15 weeks	10 days	10 days	_		x	aortic sinus
atherosclerosis diet	_	IL-1R	IL-1ra was administered by Alzet 2004 osmotic minipumps (Alza Inc) implanted in a dorsal subcutaneous pocket	human antagonist	inh	dir	0 weeks	1 month	1 month	13,5	t/m 15	x	aortic sinus
atherosclerosis diet	_	IL-1R	IL-1ra was administered by Alzet 2004 osmotic minipumps (Alza Inc) implanted in a dorsal subcutaneous pocket	human antagonist	inh	dir	0 weeks	1 month	1 month	13,5	t/m 15	x	aortic sinus
atherosclerosis diet	_	IL-1R	ip	recombinant human antagonist	inh	dir	0 weeks	7 weeks	7 weeks	19-23	16 t/m 23	x	aortic root
atherosclerosis diet	_	IL-1R	ip	recombinant human antagonist	inh	dir	0 weeks	7 weeks	7 weeks	19-23	16 t/m 23	x	aortic root
atherosclerosis diet	_	IL-1R	ip	recombinant human antagonist	inh	dir	0 weeks	12 weeks	12 weeks	24-28	24 t/m 36	x	aortic root
atherosclerosis diet	IL-1a and IL-1B	_		virus-like particle (VLP)-based vaccine	inh	dir	before diet (start seems -28 dagen, 28 days before diet), but also two boosters during diet	20 weeks +28 days	28 days, but also 2 boosters	?			
atherosclerosis diet	IL-1a and IL-1B	_		virus-like particle (VLP)-based vaccine	inh	dir	before diet (start seems -28 dagen, 28 days before diet), but also two boosters during diet	20 weeks +28 days	28 days, but also 2 boosters	?			
_	IL-1B	_	dissected segments of the coronary arteries were gently wrapped with cotton mesh and sepharose beads suspension with IL-1a or IL-1B bound	microbeads			0 weeks	2 weeks	2 weeks	11-15,5			
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	continuous infusion via subcutaneous osmotic pumps	small molecule	inh	indir	0 weeks	9 weeks	9 weeks	_		x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	continuous infusion via subcutaneous osmotic pumps	small molecule	inh	indir	0 weeks	9 weeks	9 weeks	_		x	aortic root
atherosclerosis diet	IL-1B	_	ip	antibody	inh	dir	18 weeks	8 weeks	8 weeks	34	24 t/m 36	x	whole aorta
atherosclerosis diet	IL-1B	_	sc	antibody	inh	dir	6 weeks	3 weeks	3 weeks	17-21	16 t/m 23	x	aortic root
atherosclerosis diet	IL-1B	_	sc	antibody	inh	dir	6 weeks from start diet	4 weeks	4 weeks	18- to 22	16 t/m 23	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	via tap water	inhibitor	inh	indir	6 weeks	8 weeks	8 weeks	26	24 t/m 36	x	whole aorta en face
Normal diet	IL-18	_	injected into the bilateral tibialis anterior muscles with the in vivo electroporation method	gene transfer vector	sti	dir	0 weeks tov diet. (treatment 5 times at 2-week intervals)	10 weeks	8 weeks	20	16 t/m 23	x	aortic root
atherosclerosis diet	IL-18	_	injected into the bilateral tibialis anterior muscles with the in vivo electroporation method	gene transfer vector	sti	dir	0 weeks tov diet. (treatment 5 times at 2-week intervals)	10 weeks	8 weeks	20	16 t/m 23	x	aortic root
atherosclerosis diet	IL-6	_	sc	antibody	inh	dir	7 weeks after start diet and directly after the double hit	72 h	single injection	15,42857143			
atherosclerosis diet	IL-6	_	sc	fusion protein	inh	dir	7 weeks after start diet and directly after the double hit	72 h	single injection	15,42857143			
Normal diet for 2 weeks, followed by atherosclerosis diet	IL-1B	_	ip	recombinant interleukin	sti	dir	0 weeks	~ 8 weeks	~ 8 weeks	~ 23	16 t/m 23	x	aorta roots
atherosclerosis diet	IL-1B and IL-18	Caspase-1	ip	inhibitor	inh	indir	2 weeks	10 weeks	10 weeks	18-20	16 t/m 23	x	aortic sinuses
atherosclerosis diet	IL-1B and IL-18	Caspase-1	ip	inhibitor	inh	indir	2 weeks	8 weeks	8 weeks	16-18	16 t/m 23	x	aortic roots
atherosclerosis diet	IL-1B and IL-18	Caspase-1	ip	inhibitor	inh	indir	3 weeks	10 weeks	10 weeks	19-21	16 t/m 23	x	whole aortas
atherosclerosis diet	IL-1B and IL-18	Caspase-1	ip	inhibitor	inh	indir	3 weeks	10 weeks	10 weeks	19-21	16 t/m 23	x	whole aortas
atherosclerosis diet followed by a standard laboratory diet before and during treatment	IL-1B	_	ip	antibody	inh	dir	30 weeks	8 weeks	8 weeks	47-49	47 t/m 49	x	whole aorta

Ku	2022	The Anti-Atherosclerosis Effect of Anakinra, a Recombinant Human Interleukin-1 Receptor Antagonist, in Apolipoprotein E Knockout Mice	Int. J. Mol. Sci.	English	10.3390/ijms23094906	Mice	$ApoE^{-/-}$	C57BL/6	aortic arch	m	12 weeks	Diet
Ku	2022	The Anti-Atherosclerosis Effect of Anakinra, a Recombinant Human Interleukin-1 Receptor Antagonist, in Apolipoprotein E Knockout Mice	Int. J. Mol. Sci.	English	10.3390/ijms23094906	Mice	$ApoE^{-/-}$	C57BL/6	aortic arch	m	12 weeks	Diet
Ku	2022	The Anti-Atherosclerosis Effect of Anakinra, a Recombinant Human Interleukin-1 Receptor Antagonist, in Apolipoprotein E Knockout Mice	Int. J. Mol. Sci.	English	10.3390/ijms23094906	Mice	$ApoE^{-/-}$	C57BL/6	aortic arch	m	12 weeks	Diet
Li	2021	Cytotoxin--associated gene A (CagA) promotes aortic endothelial inflammation and accelerates atherosclerosis through the NLRP3/caspase--1/IL--1β axis	FASEB J.	English	10.1096/fj.202100695RR	Mice	$ApoE^{-/-}$	C57BL/6	aortic root AND whole aorta	m	9 weeks	Diet
Li	2021	Cytotoxin--associated gene A (CagA) promotes aortic endothelial inflammation and accelerates atherosclerosis through the NLRP3/caspase--1/IL--1β axis	FASEB J.	English	10.1096/fj.202100695RR	Mice	$ApoE^{-/-}$	C57BL/6	aortic root AND whole aorta	m	9 weeks	Diet
Li	2020	Tacrolimus reduces atherosclerotic plaque formation in ApoE-/mice by inhibiting NLRP3 inflammatory corpuscles	EXPERIMENTAL AND THERAPEUTIC MEDICINE	English	10.3892/etm.2019.8340	Mice	$ApoE^{-/-}$	_	aortic root AND whole aorta	m	7 weeks	Diet
Li	2020	VX-765 attenuates atherosclerosis in ApoE deficient mice by modulating VSMCs pyroptosis	Experimental Cell Research	English	10.1016/j.yexcr.2020.111847	Mice	$ApoE^{-/-}$	_	aortic root AND whole aorta, aortic arch	m	9 weeks	Diet
Liu	2020	Macrophage K63-Linked Ubiquitination of YAP Promotes Its Nuclear Localization and Exacerbates Atherosclerosis	Cell Reports	English	10.1016/j.celrep.2020.107990	Mice	$ApoE^{-/-}$ (BM-YapTg-flox)	C57BL/6	aortic root	m	12 weeks	Diet
Liu	2023	Blockade of IL-6 signaling alleviates atherosclerosis in Tet2deficient clonal hematopoiesis	Nat Cardiovasc Res.	English	10.1038/s44161-023-00281-3.	Mice	$Ldlr^{-/-}$ (BM 40% CD45.2 Tet2loxP/loxP and 60% CD45.1 WT cells (control))	C57BL/6	aortic root	m	14-18 weeks	Diet
Luo	2020	Rutaecarpine derivative R3 attenuates atherosclerosis via inhibiting NLRP3 inflammasome-related inflammation and modulating cholesterol transport	The FASEB Journal.	English	10.1096/fj.201900903RRR	Mice	$ApoE^{-/-}$	C57BL/6	aortic sinus tissues AND en face aorta	m	8 weeks	Diet
Luo	2020	Raloxifene inhibits IL-6/STAT3 signaling pathway and protects against highfat-induced atherosclerosis in ApoE−/− mice	Life Sciences	English	10.1016/j.lfs.2020.118304	Mice	$ApoE^{-/-}$	_	aortic root AND Thoracoabdominal aorta en face (whole aorta)	m	_	Diet
Luo	2021	Bazedoxifene exhibits anti-inflammation and anti-atherosclerotic effects via inhibition of IL-6/IL-6R/STAT3 signaling	European Journal of Pharmacology	English	10.1016/j.ejphar.2020.173822	Mice	$ApoE^{-/-}$	_	aortic roots AND Thoracoabdominal aorta/total aortic surface (en face aorta)	m	6 weeks	Diet
Ma	2023	Repurposing nitazoxanide as a novel anti-atherosclerotic drug based on mitochondrial uncoupling mechanisms	Br J Pharmacol.	English	10.1111/bph.15949	Mice	$ApoE^{-/-}$	_	aortic root AND Thoracic aorta	m	8 weeks	Diet
Ma	2023	Repurposing nitazoxanide as a novel anti-atherosclerotic drug based on mitochondrial uncoupling mechanisms	Br J Pharmacol.	English	10.1111/bph.15949	Mice	$ApoE^{-/-}$	_	aortic root AND Thoracic aorta	m	8 weeks	Diet
Mallat	2001	Interleukin-18/Interleukin-18 Binding Protein Signaling Modulates Atherosclerotic Lesion Development and Stability	Circ Res.	English	10.1161/hh1901.098735	Mice	$ApoE^{-/-}$	_	aortic sinus	m	14 weeks	Spontaneous
Meng	2016	RIP3-dependent necrosis induced inflammation exacerbates atherosclerosis	Biochemical and Biophysical Research Communications	English	10.1016/j.bbrc.2016.03.059	Mice	$ApoE^{-/-}$	C57BL/6	aortic valve	m	8 weeks	Diet
Orecchioni	2022	Olfactory receptor 2 in vascular macrophages drives atherosclerosis by NLRP3-dependent IL-1 production	Science	English	10.1126/science.abg3067.	Mice	$ApoE^{-/-}$	C57BL/6J	aortic root AND en face aortic arches	m	8 to 10 weeks	Diet
Orecchioni	2022	Olfactory receptor 2 in vascular macrophages drives atherosclerosis by NLRP3-dependent IL-1 production	Science	English	10.1126/science.abg3067.	Mice	$Ldlr^{-/-}$ (BM wt)	C57BL/6J	aortic root AND en face aortic arches		12 weeks	Diet
Schuett	2012	Transsignaling of Interleukin-6 Crucially Contributes to Atherosclerosis in Mice	Arterioscler Thromb Vasc Biol.	English	10.1161/ATVBAHA.111.229435	Mice	$Ldlr^{-/-}$	C57BL/6	aortic roots AND thoracoabdominal aortas	m	10 to 12 weeks	Diet
Schuett	2012	Transsignaling of Interleukin-6 Crucially Contributes to Atherosclerosis in Mice	Arterioscler Thromb Vasc Biol.	English	10.1161/ATVBAHA.111.229435	Mice	$Ldlr^{-/-}$	C57BL/6	aortic roots AND thoracoabdominal aortas	m	10 to 12 weeks	Diet
Schuett	2012	Transsignaling of Interleukin-6 Crucially Contributes to Atherosclerosis in Mice	Arterioscler Thromb Vasc Biol.	English	10.1161/ATVBAHA.111.229435	Mice	$Ldlr^{-/-}$	C57BL/6	aortic roots AND thoracoabdominal aortas	m	10 to 12 weeks	Diet
Schwarz, N	2023	Colchicine exerts anti-atherosclerotic and -plaque-stabilizing effects targeting foam cell formation	The FASEB Journal.	English	10.1096/fj.202201469R	Mice	$ApoE^{-/-}$	C57BL/6J	En face aorta AND aortic sinus	_	8 weeks	Diet
Schwarz, N	2023	Colchicine exerts anti-atherosclerotic and -plaque-stabilizing effects targeting foam cell formation	The FASEB Journal.	English	10.1096/fj.202201469R	Mice	$ApoE^{-/-}$	C57BL/6J	carotid	_	from 6 weeks of age diet. At 12 weeks of age tandem stenosis around the right common carotid artery	Diet AND tandom stenosis
Shentu, W	2021	ECHOCARDIOGRAPHIC MOLECULAR IMAGING OF THE EFFECT OF ANTI-CYTOKINE THERAPY FOR ATHEROSCLEROSIS	J Am Soc Echocardiogr.	English	10.1016/j.echo.2020.11.012	Mice	$LDLr^{-/-}Apobec\text{-}1^{-/-}$	_	aortic root	_	?studied at 20-25 weeks	closed-chest myocardial infarction (MI)
Shimokawa	1996	Chronic Treatment with Interleukin-1β Induces Coronary Intimal Lesions and Vasospastic Responses in Pigs In Vivo	J. Clin. Invest.	English	10.1172/JCI118476	Pigs	_	_	Coronary artery	m	2-4 mo old	dissected segments of the coronary arteries were gently wrapped with a cotton mesh after absorbing 0.05 ml of Sepharose beads (Pharmacia, Uppsala, Sweden) in suspension either with or without recombinant human IL-1b
Shimokawa	1996	Chronic Treatment with Interleukin-1β Induces Coronary Intimal Lesions and Vasospastic Responses in Pigs In Vivo	J. Clin. Invest.	English	10.1172/JCI118476	Pigs	_	_	Coronary artery	m	2-4 mo old	dissected segments of the coronary arteries were gently wrapped with a cotton mesh after absorbing 0.05 ml of Sepharose beads (Pharmacia, Uppsala, Sweden) in suspension either with or without recombinant human IL-1b
Shimokawa	2001	Long-term inhibition of Rho-kinase induces a regression of arteriosclerotic coronary lesions in a porcine model in vivo	Cardiovascular Research	English	10.1016/S0008-6363%2801%290291-7	Pigs	_	_	Coronary artery	m	2-3 months old	dissected segments of the coronary arteries were applied from the adventitia with recombinant human IL-1B beads suspension absorbed in cotton mesh.
Spartalis	2021	The effect of per os colchicine administration in combination with fenofibrate and N-acetylcysteine on triglyceride levels and the development of atherosclerotic lesions in cholesterol-fed rabbits	European Review for Medical and Pharmacological Sciences	English	10.26355/eurrev_202112_27623	Rabbits	New Zealand White	Oryctolagus cuniculus	ascending aorta AND thoracic aorta and abdominal aorta	m	128 weeks (28-month-old and two weeks of acclimation)	Diet
Spartalis	2021	The effect of per os colchicine administration in combination with fenofibrate and N-acetylcysteine on triglyceride levels and the development of atherosclerotic lesions in cholesterol-fed rabbits	European Review for Medical and Pharmacological Sciences	English	10.26355/eurrev_202112_27623	Rabbits	New Zealand White	Oryctolagus cuniculus	ascending aorta AND thoracic aorta and abdominal aorta	m	128 weeks (28-month-old and two weeks of acclimation)	Diet
Takeda, N	2006	Synthetic Retinoid Am80 Reduces Scavenger Receptor Expression and Atherosclerosis in Mice by Inhibiting IL-6	Arterioscler Thromb Vasc Biol.	English	10.1161/01.ATV.0000214296.94849.1c	Mice	$ApoE^{-/-}$	hybrids of the C57Bl/6 and 129Sv strains	en face entire aorta AND aortic root		8 weeks	Diet
Tenger	2005	IL-18 Accelerates Atherosclerosis Accompanied by Elevation of IFN-γ and CXCL16 Expression Independently of T Cells	Arterioscler Thromb Vasc Biol.	English	10.1161/01.ATV.0000153516.02782.65	Mice	$SCID/ApoE^{-/-}$	C57BL/6	aortic root	f	7 weeks	_
Tian	2020	Interleukin-36 receptor antagonist attenuates atherosclerosis development by inhibiting NLRP3 inflammasome	J Cell Physiol.	English	10.1002/jcp.29813	Mice	$ApoE^{-/-}$	_	thoracoabdominal aorta AND	m	6 weeks	Diet
Tian	2020	Interleukin-36 receptor antagonist attenuates atherosclerosis development by inhibiting NLRP3 inflammasome	J Cell Physiol.	English	10.1002/jcp.29813	Mice	$ApoE^{-/-}$	_	thoracoabdominal aorta AND	m	6 weeks	Diet
Tissot	2013	A VLP-based vaccine against interleukin-1α protects mice from atherosclerosis	Eur. J. Immunol.	English	10.1002/eji.201242687	Mice	$ApoE^{-/-}$	_	aortic roots AND descending aorta en face	m	11 weeks	Diet
Tous	2006	Manipulation of inflammation modulates hyperlipidemia in apolipoprotein E-deficient mice: A possible role for interleukin-6	Cytokine	English	10.1016/j.cyto.2006.05.007	Mice	$ApoE^{-/-}$	C57BL/6	aortic root	m	12 weeks	_
Traughber	2023	Impavido attenuates inflammation, reduces atherosclerosis, and alters gut microbiota in hyperlipidemic mice	iScience	English	10.1016/j.isci.2023.106453	Mice	$ApoE^{-/-}$	C57BL/6	aortic root	f	5 weeks	Diet
Traughber	2023	Impavido attenuates inflammation, reduces atherosclerosis, and alters gut microbiota in hyperlipidemic mice	iScience	English	10.1016/j.isci.2023.106453	Mice	$ApoE^{-/-}$	C57BL/6	aortic root	m	5 weeks	Diet
van der Heijden	2017	NLRP3 Inflammasome Inhibition by MCC950 Reduces Atherosclerotic Lesion Development in Apolipoprotein E–Deficient Mice—Brief Report	Arterioscler Thromb Vasc Biol.	English	10.1161/ATVBAHA.117.309575.	Mice	$ApoE^{-/-}$	_	carotid artery	f	_	semiconstrictive perivascular collar placement at the carotid arteries
Vromman	2019	Stage-dependent differential effects of interleukin-1 isoforms on experimental atherosclerosis	European Heart Journal	English	10.1093/eurheartj/ehz133	Mice	$ApoE^{-/-}$	C57BL/6	aortic root AND in the brachiocephalic artery	m	8 weeks	Diet
Vromman	2019	Stage-dependent differential effects of interleukin-1 isoforms on experimental atherosclerosis	European Heart Journal	English	10.1093/eurheartj/ehz133	Mice	$ApoE^{-/-}$	C57BL/6	aortic root AND in the brachiocephalic artery	m	8 weeks	Diet
Vromman	2019	Stage-dependent differential effects of interleukin-1 isoforms on experimental atherosclerosis	European Heart Journal	English	10.1093/eurheartj/ehz133	Mice	$ApoE^{-/-}$	C57BL/6	aortic root AND in the brachiocephalic artery	m	8 weeks	Diet
Vromman	2019	Stage-dependent differential effects of interleukin-1 isoforms on experimental atherosclerosis	European Heart Journal	English	10.1093/eurheartj/ehz133	Mice	$ApoE^{-/-}$	C57BL/6	aortic root AND in the brachiocephalic artery	m	8 weeks	Diet
Vromman	2019	Stage-dependent differential effects of interleukin-1 isoforms on experimental atherosclerosis	European Heart Journal	English	10.1093/eurheartj/ehz133	Mice	$ApoE^{-/-}$	C57BL/6	aortic root AND in the brachiocephalic artery	m	8 weeks	Diet
Vromman	2019	Stage-dependent differential effects of interleukin-1 isoforms on experimental atherosclerosis	European Heart Journal	English	10.1093/eurheartj/ehz133	Mice	$ApoE^{-/-}$	C57BL/6	aortic root AND in the brachiocephalic artery	m	8 weeks	Diet
Wan, Z	2019	NLRP3 inflammasome promotes diabetes-induced endothelial inflammation and atherosclerosis	Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy	English	10.2147/DMSO.S222053	Mice	$ApoE^{-/-}$	_	aortic root	_	6 weeks	Diet
Wang	2020	Thioredoxin-1 attenuates atherosclerosis development through inhibiting NLRP3 inflammasome	Endocrine	English	10.1007/s12020-020-02389-z	Mice	$ApoE^{-/-}$	C57BL/6	whole aorta	m	6 weeks	Diet
Wen	2020	Tanshinone IIA attenuates atherosclerosis via inhibiting NLRP3 inflammasome activation	Aging	English	10.18632/aging.202202	Mice	$ApoE^{-/-}$	C57BL/6	relative lesion area of cross-section (mm^2) (of AS in the aorta)	m	7 weeks	Diet
Wen	2020	Tanshinone IIA attenuates atherosclerosis via inhibiting NLRP3 inflammasome activation	Aging	English	10.18632/aging.202202	Mice	$ApoE^{-/-}$	C57BL/6	entire aorta from brachiocephalic artery to iliac artery bifurcation	m	7 weeks	Diet

atherosclerosis diet	_	IL-1R	ip	recombinant human antagonist	inh	dir	minus 4 weeks	16 weeks	16 weeks	24	24 t/m 36	x	aortic arch en face
atherosclerosis diet	_	IL-1R	ip	recombinant human antagonist	inh	dir	minus 4 weeks	16 weeks	16 weeks	24	24 t/m 36	x	aortic arch en face
atherosclerosis diet	_	IL-1R	ip	recombinant human antagonist	inh	dir	minus 4 weeks	16 weeks	16 weeks	24	24 t/m 36	x	aortic arch en face
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	ip	small molecule	inh	indir	0 weeks	6 weeks	6 weeks	15	t/m 15	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	ip	small molecule+recombinant antigen			0 weeks	6 weeks	6 weeks	15			
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	ip	immunosuppressor	inh	indir	6 weeks	12 weeks	12 weeks	25	24 t/m 36	x	aortic root
atherosclerosis diet	IL-1B and IL-18	Caspase-1	intragastric gavage	inhibitor	inh	indir	8 weeks	6 weeks	6 weeks	23	16 t/m 23	x	aortic root
atherosclerosis diet	_	IL-1R	ip	recombinant human antagonist	inh	dir	0 weeks	6 weeks	6 weeks	18	16 t/m 23	x	aortic root
atherosclerosis diet	_	IL-6R	ip	antibody	inh	dir	2 weeks	10 weeks	10 weeks	26-30	24 t/m 36	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	gastric gavage	derivative of natural product	inh	indir	0 weeks	12 weeks	12 weeks	20	16 t/m 23	x	aortic root
atherosclerosis diet	IL-6	_	intragastric gavage	small molecule	inh	indir	_	_	_	_	_	x	whole aortic sinus
atherosclerosis diet	IL-6	_	1 week before High-fat diet were mice treated with bazedoxifene by oral gavage followed by 12 weeks High-fat diet combined with bazedoxifene	small molecule	inh	indir	minus 1 week	13 weeks	13 weeks	18	16 t/m 23	x	aortic sinus (aortic root)
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	intragastrically administered	oral antiprotozoal drug	inh	indir	0 weeks	15 weeks	15 weeks	23	16 t/m 23	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	intragastrically administered	oral antiprotozoal drug	inh	indir	0 weeks	15 weeks	15 weeks	23	16 t/m 23	x	aortic root
_	IL-18	_	in vivo intramuscular electrotransfer of an expression-plasmid DNA encoding for isoform d of murine IL-18BP	expression-plasmid DNA	inh	dir	0 weeks	9 weeks	9 weeks	23	16 t/m 23	x	aortic sinus
atherosclerosis diet	IL-1a	_	ip	antibody	inh	dir	8 weeks	8 weeks	8 weeks	24	24 t/m 36	x	aortic valve
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	ip	aliphatic aldehyde	sti	indir	4 weeks	4 weeks	4 weeks	16 to 18	16 t/m 23	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	ip	aliphatic aldehyde	sti	indir	8 weeks	4 weeks	4 weeks	24	24 t/m 36	x	aortic root
atherosclerosis diet	IL-6	_	ip	inhibitor	inh	dir	0 weeks	8 weeks	8 weeks	18 to 20	16 t/m 23	x	aortic root
atherosclerosis diet	IL-6	_	ip	inhibitor	inh	dir	0 weeks	16 weeks	16 weeks	26 to 28	24 t/m 36	x	aortic root
atherosclerosis diet	IL-6	_	ip	inhibitor	inh	dir	12 weeks	12 weeks	12 weeks	34 to 36	24 t/m 36	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	oral gavage	colchicine	inh	indir	4 weeks	12 weeks	12 weeks	24	24 t/m 36	x	aortic sinus
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	added to drinking water ad libitum	colchicine	inh	indir	6 weeks after start diet and immediately after surgery	7 weeks	7 weeks	19			
Normal diet	IL-1B	_	ip	antibody			immediately before ischemia (0), on day 2, 4, 11 and 18 after MI	21 days	18 days	_			
_	IL-1B	_	dissected segments of the coronary arteries were gently wrapped with a cotton mesh after absorbing 0.05 ml of Sepharose beads (Pharmacia, Uppsala, Sweden) in suspension either with or without recombinant human IL-1b	beads			0 weeks	every week for 4 weeks	4 weeks (coronary anteriographic study every week for 4 weeks)	10-17, 11-18, 12-19, 13-20			
_	IL-1B	_	dissected segments of the coronary arteries were gently wrapped with a cotton mesh after absorbing 0.05 ml of Sepharose beads (Pharmacia, Uppsala, Sweden) in suspension either with or without recombinant human IL-1b	beads			0 weeks	2 weeks	2 weeks	11 - 18			
_	IL-1B	_	dissected segments of the coronary arteries were applied from the adventitia with recombinant human IL-1B beads suspension absorbed in cotton mesh. And fasudil oral administration				0 weeks for IL-1Beta beads and 2 weeks for fasudil.	for fasudil: 0 weeks (before fasudil treatment) , 4 weeks fasudil, 8 weeks fasudil, 9 weeks (from which 8 weeks fasudil)	total 8 weeks fasudil treatment	11-15,5, 15-19,5, 19-23,5, 20-24,5			
atherosclerosis diet	IL-6. IL-1B and IL-18	NLRP3 inflammasome	in tap water	natural product + ligand			0 weeks	7 weeks	7 weeks	135			
atherosclerosis diet	IL-6. IL-1B and IL-18	NLRP3 inflammasome	in tap water	natural product + cysteine derivative			0 weeks	7 weeks	7 weeks	135			
atherosclerosis diet	IL-6	_	orally administered	synthetic agonist	inh	indir	0 weeks	2 months	2 months	17	16 t/m 23	x	aortic sinus
Normal diet	IL-18	_	ip	recombinant mouse interleukin	sti	dir	0 weeks	7 weeks	7 weeks	14	t/m 15	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	iv	lentivirus expressing antagonist	inh	indir	4 weeks	12 weeks	12 weeks	22	16 t/m 23	x	thoracoabdominal aorta
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	iv	lentivirus expressing antagonist + interleukin			4 weeks	12 weeks	12 weeks	22			
atherosclerosis diet	IL-1a	_	sc	vaccine	inh	dir	minus 3 weeks	(159/7) weeks	160 days	30,71428571	24 t/m 36	x	root of the aorta
commercial mouse diet (B&K Universal, N. Humberside, UK)	IL-6	_	ip	recombinant mouse interleukin	sti	dir	0 weeks	12 weeks	12 weeks	24	24 t/m 36	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	diet	drug	inh	indir	0 weeks	9 weeks	3 weeks	14	t/m 15	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	diet	drug	inh	indir	0 weeks	9 weeks	3 weeks	14	t/m 15	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	ip	small molecule			0 weeks	4 weeks	4 weeks	_			
atherosclerosis diet	IL-1a	_	sc	antibody	inh	dir	0 weeks	28 weeks	28 weeks	36	24 t/m 36	x	aortic root
atherosclerosis diet	IL-1B	_	sc	antibody	inh	dir	0 weeks	28 weeks	28 weeks	36	24 t/m 36	x	aortic root
atherosclerosis diet	IL-1a and IL-1B	_	sc	antibody			0 weeks	28 weeks	28 weeks	36			
atherosclerosis diet	IL-1a	_	sc	antibody	inh	dir	14 weeks	14 weeks	14 weeks	36	24 t/m 36	x	aortic root
atherosclerosis diet	IL-1B	_	sc	antibody	inh	dir	14 weeks	14 weeks	14 weeks	36	24 t/m 36	x	aortic root
atherosclerosis diet	IL-1a and IL-1B	_	sc	antibody			14 weeks	14 weeks	14 weeks	36			
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	iv	lentivirus	inh	indir	12 days	14 weeks and 2 days	4 weeks	22	16 t/m 23	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	iv	lentivirus	inh	indir	4 weeks	12 weeks	Once	22	16 t/m 23	x	in the aorta
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	diet?	natural product	inh	indir	0 weeks	_	_	_		x	cross-section (of AS in the aorta)
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	diet?	natural product			0 weeks	_	_	_			

Wen	2020	Tanshinone IIA attenuates atherosclerosis via inhibiting NLRP3 inflammasome activation	Aging	English	10.18632/aging.202202	Mice	$ApoE^{-/-}$	C57BL/6	entire aorta from brachiocephalic artery to iliac artery bifurcation	m	7 weeks	Diet
Wen	2020	Tanshinone IIA attenuates atherosclerosis via inhibiting NLRP3 inflammasome activation	Aging	English	10.18632/aging.202202	Mice	$ApoE^{-/-}$	C57BL/6	entire aorta from brachiocephalic artery to iliac artery bifurcation	m	7 weeks	Diet
Whitman	2002	Interleukin-18 Enhances Atherosclerosis in Apolipoprotein E-/- Mice Through Release of Interferon-γ	Circ Res.	English	10.1161/hh0202.105292	Mice	$ApoE^{-/-}$	_	ascending aorta AND the aortic arch	m	16 weeks	_
Whitman	2002	Interleukin-18 Enhances Atherosclerosis in Apolipoprotein E-/- Mice Through Release of Interferon-γ	Circ Res.	English	10.1161/hh0202.105292	Mice	ifn-$\gamma^{-/-}$/$ApoE^{-/-}$	_	ascending aorta AND the aortic arch	m	16 weeks	_
Wu, X	2022	Pharmacological inhibition of IRAK1 and IRAK4 prevents endothelial inflammation and atherosclerosis in ApoE-/- mice	Pharmacological Research	English	10.1016/j.phrs.2021.106043	Mice	$ApoE^{-/-}$	_	en face aorta AND aortic root		8 weeks	Diet
Xie	2021	SNF5 promotes IL-1β expression via H3K4me1 in atherosclerosis induced by homocysteine	International Journal of Biochemistry and Cell Biology	English	10.1016/j.biocel.2021.105974	Mice	$ApoE^{-/-}$	_	aortic root	m	6 weeks	_
Xu	2021	circDENND1B Participates in the Antiatherosclerotic Effect of IL-1β Monoclonal Antibody in Mouse by Promoting Cholesterol Efflux via miR-17-5p/Abca1 Axis	Frontiers in Cell and Developmental Biology	English	10.3389/fcell.2021.652032	Mice	$ApoE^{-/-}$	C57BL/6	aortic root	m	6 weeks	Diet
Xu	2023	A metal-organic framework-based immunomodulatory nanoplatform for anti-atherosclerosis treatment	Journal of Controlled Release	English	10.1016/j.jconrel.2023.01.024	Mice	$ApoE^{-/-}$	_	whole aortas AND coronary arteries and carotid arteries	m	5-6 weeks	Left common carotid arteries were constricted with a small silica collar and diet
Xu	2023	A metal-organic framework-based immunomodulatory nanoplatform for anti-atherosclerosis treatment	Journal of Controlled Release	English	10.1016/j.jconrel.2023.01.024	Mice	$ApoE^{-/-}$	_	whole aortas AND coronary arteries and carotid arteries	m	5-6 weeks	Left common carotid arteries were constricted with a small silica collar and diet
Xu	2023	A metal-organic framework-based immunomodulatory nanoplatform for anti-atherosclerosis treatment	Journal of Controlled Release	English	10.1016/j.jconrel.2023.01.024	Mice	$ApoE^{-/-}$	_	whole aortas AND coronary arteries and carotid arteries	m	5-6 weeks	Left common carotid arteries were constricted with a small silica collar and diet
Yalcinkaya	2023	Cholesterol accumulation in macrophages drives NETosis in atherosclerotic plaques via IL-1β secretion	Cardiovascular Research	English	10.1093/cvr/cvac189	Mice	$Ldlr^{-/-}$ (BM from LysmCreAbca1fl/flAbcg1fl/fl (Myl-Abcdko))	_	aortic root	f	8 weeks	Diet
Zhang	2012	Interleukin 6 destabilizes atherosclerotic plaques by downregulating prolyl-4-hydroxylase a1 via a mitogen-activated protein kinase and c-Jun pathway	Archives of Biochemistry and Biophysics	English	10.1016/j.abb.2012.09.007	Mice	$ApoE^{-/-}$	_	carotid	m	8 weeks	perivascular constrictive silica collar placement on the right common carotid artery
Zhao	2020	Baicalin ameliorates atherosclerosis by inhibiting NLRP3 inflammasome in apolipoprotein E-deficient mice	Diabetes & Vascular Disease Research	English	10.1177/1479164120977441	Mice	$ApoE^{-/-}$	_	aortic root	m	8 weeks	Diet
Zhao	2020	Baicalin ameliorates atherosclerosis by inhibiting NLRP3 inflammasome in apolipoprotein E-deficient mice	Diabetes & Vascular Disease Research	English	10.1177/1479164120977441	Mice	$ApoE^{-/-}$	_	aortic root	m	8 weeks	Diet
Zhao	2020	Baicalin ameliorates atherosclerosis by inhibiting NLRP3 inflammasome in apolipoprotein E-deficient mice	Diabetes & Vascular Disease Research	English	10.1177/1479164120977441	Mice	$ApoE^{-/-}$	_	aortic root	m	8 weeks	Diet
Zhao	2020	Baicalin ameliorates atherosclerosis by inhibiting NLRP3 inflammasome in apolipoprotein E-deficient mice	Diabetes & Vascular Disease Research	English	10.1177/1479164120977441	Mice	$ApoE^{-/-}$	_	aortic root	m	8 weeks	Diet

atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	diet?	natural product			0 weeks	_	_	_			
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	diet?	natural product			0 weeks	_	_	_			
Normal diet	IL-18	_	ip	recombinant interleukin	sti	dir	0 weeks	30 days	30 days	20,28571429	16 t/m 23	x	ascending aorta
Normal diet	IL-18	_	ip	recombinant interleukin	sti	dir	0 weeks	30 days	30 days	20,28571429	16 t/m 23	x	ascending aorta
atherosclerosis diet	_	IL-1R	orally administered	inhibitor	inh	indir	0 weeks	8 weeks	8 weeks	16	16 t/m 23	x	aortic sinus
Control: Normal diet. Other group: 1.7% methionine diet (Hhcy)	IL-1B	_	diet	sulphur-containing amino acid	sti	indir	0 weeks	_	_	_		x	aorta roots
atherosclerosis diet	IL-1B	_	ip	antibody			6 weeks	6 weeks	6 weeks	18			
atherosclerosis diet	_	IL-1R	iv	antagonist	inh	dir	8 weeks	4 weeks	4 weeks	17-18	16 t/m 23	x	among whole aorta areas
atherosclerosis diet	_	IL-1R	iv	nanoparticles +antaganoist			8 weeks	4 weeks	4 weeks	17-18			
atherosclerosis diet	_	IL-1R	iv	nanoparticles +antaganoist +rapamycine			8 weeks	4 weeks	4 weeks	17-18			
atherosclerosis diet	IL-1B	_	sc	antibody	inh	dir	6 weeks	2,5 weeks	2,5 weeks (3x injectie)	16,5	16 t/m 23	x	aortic root
atherosclerosis diet	IL-6	_	lentiviral suspension instilled into the right common carotid artery	lentivirus			6 weeks	2 weeks	2 weeks	16			
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	iv	lentivirus	inh	indir	4 weeks	8 weeks	8 weeks	20	16 t/m 23	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	intragastrically injected	natural product	inh	indir	4 weeks	8 weeks	8 weeks	20	16 t/m 23	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	intragastrically injected	natural product	inh	indir	4 weeks	8 weeks	8 weeks	20	16 t/m 23	x	aortic root
atherosclerosis diet	IL-1B and IL-18	NLRP3 inflammasome	intragastrically injected	natural product	inh	indir	4 weeks	8 weeks	8 weeks	20	16 t/m 23	x	aortic root

Supplementary Table 5. Reporting quality information.

Paper	Any experiment randomization	Any experiment blinding	Reporting of power/ sample size calculation	Reporting of conflict of interest statement	Prespecified/ preregistered protocol
Abderrazak et al., 2015	Y	N	N	Y	N
Akita et al., 2017	N	Y	N	Y	N
Bhaskar et al., 2011	N	N	N	N	N
Bhat et al., 2015	N	Y	N	Y	N
Bhat et al., 2018	N	Y	N	Y	N
Chen S et al., 2012	N	Y	N	Y	N
Chen J et al., 2022	Y	N	N	Y	N
Christersdottir et al., 2019	N	N	N	Y	N
de Nooijer et al., 2004	N	N	N	N	N
Denes et al., 2012	N	Y	N	Y	N
Dragoljevic et al., 2020	Y	Y	N	Y	N
Elhage et al., 1998	N	N	N	N	N
Fidler et al., 2021	Y	Y	Y	N	N
Freigang et al., 2011	N	N	N	Y	N
Fukumoto et al., 1997	Y	Y	N	N	N
Fuster et al., 2017	N	Y	N	N	N
Gomez et al., 2018	Y	Y	Y	N	N
Hettwer et al., 2022	Y	N	N	Y	N
Hohensinner et al., 2021	Y	Y	N	Y	N
Imai et al., 2011	N	Y	N	N	N
Janssen et al., 2015	N	Y	N	Y	N
Jia et al., 2023	Y	N	N	Y	N
Jin et al., 2022	Y	Y	N	Y	N
Karnewar et al., 2024	Y	Y	N	Y	N
Ku et al., 2022	Y	N	N	Y	N
Li B et al., 2021	N	N	N	Y	N
Li X et al., 2020	N	N	N	Y	N
Li Y et al., 2020	N	N	N	Y	N
Liu M et al., 2020	N	Y	N	Y	N
Liu W et al., 2023	Y	N	N	Y	N
Luo J et al., 2020	Y	N	N	Y	N
Luo P et al., 2020	Y	N	N	Y	N
Luo P et al., 2021	Y	N	N	Y	N
Ma et al., 2023	Y	Y	N	Y	N
Mallat et al., 2001	N	Y	N	N	N
Meng et al., 2016	N	N	N	Y	N
Orecchioni et al., 2022	N	Y	Y	Y	N
Schuett et al., 2012	Y	N	N	Y	N
Schwarz et al., 2023	Y	Y	N	Y	N
Shentu et al., 2021	Y	N	N	Y	N
Shimokawa et al., 1996	Y	N	N	N	N
Shimokawa et al., 2001	Y	Y	N	N	N
Spartalis et al., 2021	Y	Y	N	Y	N
Takeda et al., 2006	N	N	N	N	N
Tenger et al., 2005	Y	Y	N	N	N
Tian et al., 2020	N	N	N	Y	N
Tissot et al., 2013	N	Y	N	Y	N

Tous et al., 2006	N	N	N	N	N
Traughber et al., 2023	N	N	N	Y	N
van der Heijden et al., 2017	N	Y	N	Y	N
Vromman et al., 2019	Y	Y	N	Y	N
Wan et al., 2019	Y	N	N	Y	N
Wang et al., 2020	N	N	N	Y	N
Wen et al., 2021	N	N	N	Y	N
Whitman et al., 2002	N	N	N	N	N
Wu et al., 2022	N	N	N	Y	N
Xie et al., 2021	Y	N	N	Y	N
Xu F et al., 2021	Y	N	N	Y	N
Xu Z et al., 2023	Y	N	N	Y	N
Yalcinkaya et al., 2023	N	N	Y	Y	N
Zhang et al., 2012	N	N	N	N	N
Zhao et al., 2020	N	Y	N	Y	N

Supplementary Table 6. Risk of bias information.

	Selection bias			Performance bias		Detection bias		Attrition bias	Reporting bias	Other
Paper	Allocation sequence generation and application	Baseline characteristics	Allocation concealment	Random housing	Caregivers/ investigators blinded during experiment	Random outcome assessment	Outcome assessment blinded	Incomplete outcome data addressed	Selective outcome reporting	Other risks of bias
Abderrazak et al., 2015	?	Y	?	?	?	?	?	N	N	Y
Akita et al., 2017	?	?	?	?	?	?	Y	?	Y	Y
Bhaskar et al., 2011	?	Y	?	?	?	?	?	?	Y	N
Bhat et al., 2015	?	Y	?	?	?	?	Y	Y	Y	N
Bhat et al., 2018	?	Y	?	?	?	?	Y	Y	Y	Y
Chen S et al., 2012	?	Y	?	?	?	?	Y	N	N	Y
Chen J et al., 2022	?	Y	?	N	N	?	?	Y	Y	Y
Christersdottir et al., 2019	?	Y	?	?	N	?	?	N	Y	Y
de Nooijer et al., 2004	?	Y	?	?	?	?	?	?	Y	N
Denes et al., 2012	?	Y	?	?	?	?	Y	N	Y	Y
Dragoljevic et al., 2020	?	?	?	?	Y	?	Y	N	Y	Y
Elhage et al., 1998	?	Y	?	?	?	?	?	?	Y	Y
Fidler et al., 2021	?	N	?	?	?	?	Y	N	N	Y
Freigang et al., 2011	?	Y	?	?	?	?	?	?	Y	N
Fukumoto et al., 1997	?	Y	?	Y	?	?	?	N	Y	?
Fuster et al., 2017	?	N	?	?	?	?	Y	?	Y	Y
Gomez et al., 2018	?	Y	?	?	Y	?	Y	Y	Y	Y
Hettwer et al., 2022	?	N	?	?	?	?	?	?	?	Y
Hohensinner et al., 2021	?	Y	?	?	N	?	Y	N	Y	Y
Imai et al., 2011	?	Y	?	?	?	?	Y	N	Y	Y
Janssen et al., 2015	?	Y	N	?	?	?	Y	Y	Y	Y
Jia et al., 2023	?	Y	?	?	?	?	?	Y	Y	Y
Jin et al., 2022	?	Y	?	?	?	?	Y	N	Y	N
Karnewar et al., 2024	?	?	?	?	Y	?	Y	?	Y	Y
Ku et al., 2022	Y	Y	?	?	?	?	?	?	Y	Y
Li B et al., 2021	?	Y	?	?	?	?	?	?	N	Y
Li X et al., 2020	?	Y	?	?	N	?	?	?	Y	Y
Li Y et al., 2020	?	Y	?	?	?	?	?	?	Y	N
Liu M et al., 2020	?	Y	?	?	?	?	Y	N	Y	Y
Liu W et al., 2023	?	Y	?	?	?	?	?	N	Y	Y
Luo J et al., 2020	?	Y	?	?	?	?	?	?	Y	Y

Luo P et al., 2020	?	Y	?	?	?	?	?	?	Y	Y
Luo P et al., 2021	?	Y	?	?	?	?	?	Y	Y	Y
Ma et al., 2023	?	Y	?	?	?	?	Y	?	Y	Y
Mallat et al., 2001	?	Y	?	?	?	?	Y	Y	Y	Y
Meng et al., 2016	?	Y	?	?	?	?	?	?	Y	N
Orecchioni et al., 2022	?	Y	?	?	?	?	Y	N	Y	Y
Schuett et al., 2012	?	Y	?	?	?	?	?	N	Y	Y
Schwarz et al., 2023	?	?	?	?	?	?	Y	?	Y	Y
Shentu et al., 2021	?	?	?	?	?	?	?	?	N	Y
Shimokawa et al., 1996	?	N	?	?	?	?	?	Y	N	N
Shimokawa et al., 2001	?	N	?	?	N	?	Y	N	Y	Y
Spartalis et al., 2021	?	Y	?	Y	N	?	Y	Y	Y	Y
Takeda et al., 2006	?	?	?	?	?	?	?	?	N	N
Tenger et al., 2005	?	Y	?	?	?	?	Y	N	Y	Y
Tian et al., 2020	?	Y	?	?	?	?	?	Y	Y	Y
Tissot et al., 2013	?	Y	?	?	?	?	Y	N	Y	Y
Tous et al., 2006	?	Y	?	?	?	?	?	?	Y	Y
Traughber et al., 2023	?	Y	?	N	N	?	?	N	Y	Y
van der Heijden et al., 2017	?	?	?	?	?	?	Y	?	Y	Y
Vromman et al., 2019	?	Y	?	?	N	?	Y	N	Y	?
Wan et al., 2019	?	?	?	?	?	?	?	Y	Y	Y
Wang et al., 2020	?	Y	?	?	?	?	?	Y	Y	Y
Wen et al., 2021	?	Y	?	?	N	?	?	?	N	N
Whitman et al., 2002	?	Y	?	?	?	?	?	N	Y	Y
Wu et al., 2022	?	?	?	?	?	?	?	N	Y	Y
Xie et al., 2021	?	Y	?	N	N	?	?	?	Y	Y
Xu F et al., 2021	?	Y	?	?	?	?	?	?	Y	N
Xu Z et al., 2023	?	Y	?	?	?	?	?	Y	Y	N
Yalcinkaya et al., 2023	?	Y	?	?	?	?	?	?	Y	Y
Zhang et al., 2012	?	Y	?	?	?	?	?	Y	Y	Y
Zhao et al., 2020	?	Y	?	?	?	?	Y	?	Y	Y

Supplementary Table 7. Plaque size data and intervention for meta-analysis comparisons. For each comparison the lesion size, SD (standard deviation), unit and sample size (n) are displayed for both the control and the treatment group. Also, the type of immunomodulatory component, whether this component is inhibitory or stimulatory and which molecule it targets are shown for every comparison.

Paper	Control	Mean lesion size: control	SD	n	Treatment	Mean lesion size: treated	SD	n	Unit	Type of intervention
Inhibitory intervention										
Bhaskar et al., 2011	mIgG	25,42	7,74	10	0.1 mg/kg XMA052MG 1K	15,89	5,05	10	%	IL-1β antibody
	mIgG	25,42	7,74	10	1.0 mg/kg XMA052MG 1K	19,76	5,29	10	%	
	mIgG	25,42	7,74	10	10 mg/kg XMA052MG 1K	17,99	4,61	7	%	
Chen S et al., 2012	Lactobacillus casei cell wall extract (LCWE)	413747	85237	10	LCWE+IL1-RA	216981	76713	10	μm^2	Recombinant human IL-1R antagonist
Christersdottir et al., 2019	Control: sodium chloride	19,39	3,84	7	Anakinra	14,71	2,51	7	%	Recombinant human IL-1R antagonist
Denes et al., 2012	Anti–cyclosporin A isotype control antibody + Paigen diet	0,20	0,12	13	IL-1β antibody + Paigen diet	0,14	0,06	11	Ratio	IL-1β antibody
	Anti–cyclosporin A isotype control antibody + High-fat diet	0,16	0,05	7	IL-1β antibody + High-fat diet	0,13	0,05	8	Ratio	
Dragoljevic et al., 2020	Vehicle	376923	152300	8	Anakinra	289744	40704	7	μm^2	Recombinant human IL-1R antagonist
Elhage et al., 1998	BSA (25 mg /kg body wt/d)	247801	89387	7	IL-1RA (female)	92501	29592	6	μm^2	Human IL-1R antagonist
	BSA (25 mg /kg body wt/d)	152342	53343	6	IL-1RA (male)	66744	10452	6	μm^2	
Fidler et al., 2021	Saline	54824	19555	8	Anakinra	50861	22226	8	μm^2	Recombinant human IL-1R antagonist (in different mouse models)
	Saline	109167	113837	7	Anakinra	92688	57221	9	μm^2	
	Saline	443840	95933	24	Anakinra	461662	109379	25	μm^2	
Fuster et al., 2017	PBS	299500	77660	10	MCC950	237900	49160	9	μm^2	NLRP3 inflammasome small molecule inhibitor (in different mouse models)
	PBS	389000	95550	8	MCC950	197000	59100	10	μm^2	
Gomez et al., 2018	IgG control	0,44	0,13	6	IL-1β Ab	0,45	0,08	6	%	IL-1β antibody
Hohensinner et al., 2021	Control	9,6	2	13	Trimetazidine	6,3	1,3	13	%	NLRP3 inflammasome inhibitor
Hettwer et al., 2022	Ctrl IgG	182895	92511	13	IL-1β Ab	114474	58914	11	μm^2	Murine analogue of canakinumab
	Ctrl IgG	333990	92149	12	IL-1β Ab	247291	78423	11	μm^2	
Jin et al., 2022	DM	59	15	3	VX	29	4	3	mm^2	VX765 caspase 1 inhibitor (different vascular locations)
	DM	17	3	4	VX	7	2	4	mm^2	
	DM	8,74	2,34	5	VX	4,52	2,69	4	%	
	DM	5,99	0,99	9	VX	5,21	0,93	7	%	

Karnewar et al., 2024	IgG	18,08	15,16	5	IL-1B Ab	62,90	19,37	5	%	IL-1β antibody
Ku et al., 2022	Control	100	29,29	10	Anakinra 10 mg/kg/day	108,42	38,61	10	%	Recombinant human IL-1R antagonist
	Control	100	29,29	10	Anakinra 25 mg/kg/day	69,26	11,32	10	%	
	Control	100	29,29	10	Anakinra 50 mg/kg/day	74,53	19,31	10	%	
Li B et al., 2021	PBS	166143	49868	7	MCC950	122164	35092	7	μm^2	NLRP3 inflammasome small molecule inhibitor
Li X et al., 2020	$ApoE^{-/-}$	20,05	1,55	10	$ApoE^{-/-}$ + Tac	14,08	0,78	10	%	NLRP3 inflammasome inhibition
Li Y et al., 2020	vehicle	390311	114461	5	VX-765	362888	63362	5	μm^2	Caspase-1 inhibitor
Liu M et al., 2020	PBS	168481	72488	10	Anakinra	100287	83361	10	μm^2	Recombinant human IL-1R antagonist
Liu W et al., 2023	Control	215385	44772	14	Anti-IL-6R	240171	82756	15	μm^2	IL-6R antibody
Luo J et al., 2020	Model control	318491	19968	7	R3	212830	19968	7	μm^2	Natural product: NLRP3 inflammasome inhibitor
Luo P et al., 2020	HFD	0,44	0,02	4	HFD + RA	0,24	0,05	4	%	Small molecule IL-6 inhibitor
Luo P et al., 2021	HFD	32,26	1,89	6	HFD + Bazedoxifene	19,51	1,65	6	%	small molecule IL-6 inhibitor
Ma et al., 2023	WD	444985	127375	14	WD + Nit100	272340	72786	14	μm^2	NLRP3 inflammasome inhibition
	WD	444985	127375	14	WD + Nit200	213982	72786	14	μm^2	
Mallat et al., 2001	Empty plasmid	285609	96507	19	IL-18BP plasmid	215498	66273	14	μm^2	Expression-plasmid DNA encoding for murine IL-18 binding protein (BP)
Meng et al., 2016	IgG	16262626	1818182	9	Anti-IL-1α antibody	12222222	909091	9	μm^2	IL-1α antibody
Schuett et al., 2012	8 weeks control	13,86	4,75	5	8 weeks sgp130Fc	10,18	2,81	7	%	IL-6 inhibitor
	16 weeks control	37,5	2,67	6	16 weeks sgp130Fc	25,12	3,96	9	%	
	Advanced 12 weeks control	27,48	3,36	10	Advanced 12 weeks sgp130Fc	17,34	6,62	8	%	
Schwarz et al., 2023	PBS	133912	59148	11	COL	127287	39748	12	μm^2	Colchicine
Takeda et al., 2006	Vehicle	206429	12352	8	Am80	149021	19282	8	μm^2	IL-6 inhibitor
Tian et al., 2020	GFP (lentivirus)	14,67	8,04	8	IL-36RN (lentivirus)	4,89	3,92	8	%	Lentivirus expressing NLRP3 inflammasome antagonist
Tissot et al., 2013	Qb	466769	115803	11	IL-1a-Qb	293109	72884	13	μm^2	IL-1α vaccine
Traughber et al., 2023	Females WTD	169629	37867	9	Females MF	82303	25889	9	μm^2	NLRP3 inflammasome inhibition
	Males WTD	137595	22222	9	Males MF	68189	13699	9	μm^2	
Vromman et al., 2019	Atherogenesis control	593651	139683	13	Atherogenesis Anti-IL-1α	447619	92063	13	μm^2	IL-1α antibody
	Atherogenesis control	593651	139683	13	Atherogenesis Anti-IL-1β	590476	130159	13	μm^2	IL-1β antibody
	Established atheromata control	361371	119626	16	Established atheromata Anti-IL-1α	338941	79751	16	μm^2	IL-1α antibody

	Established atheromata control	361371	119626	16	Established atheromata Anti-IL-1β	271651	119626	16	μm^2	IL-1β antibody
Wan et al., 2019	Scramble shRNA	45,49	4,28	10	NLRP3 shRNA	25,40	2,20	10	%	shRNA lentivirus
Wang et al., 2020	GFP (lentivirus)	15,53	5,79	8	Trx-1 (lentivirus)	5,08	1,80	8	%	Trx-1 lentivirus: NLRP3 inflammasome inhibition
Wen et al., 2021	HCh diet	15322581	3744240	8	HCh diet/Tan IIA-20	4896313	1094470	8	μm^2	natural product: NLRP3 inflammasome inhibition
Wu et al., 2022	Control	50,54	9,11	5	IRAK1/4i	38,54	7,69	9	%	Dual IL-1R-associated kinase 1 and 4 inhibitor
Xu Z et al., 2023	Saline	11,36	0,84	3	IL-1RA	7,09	0,84	3	%	IL-1R antagonist
Yalcinkaya et al., 2023	IgG control	203497	62293	14	IL-1β antibody	174126	59584	16	μm^2	IL-1β antibody
Zhao et al., 2020	AS + sh-Control	350937	44293	7	AS + sh-NLRP3	188245	34923	7	μm^2	Lentivirus: NLRP3 inflammasome inhibition
	AS	350090	47576	7	20 mg/kg baicalin	342908	52065	7	μm^2	
	AS	350090	47576	7	50 mg/kg baicalin	263016	52065	7	μm^2	
	AS	350090	47576	7	100 mg/kg baicalin	202873	45781	7	μm^2	
Stimulatory intervention										
Bhat et al., 2018	Control	1,52	0,57	6	IL-18	24,09	13,32	6	%	Recombinant mouse IL-18
Imai et al., 2011	Control (chow)	35,45	15,76	11	IL-18 (chow)	39,80	11,27	10	%	IL-18 gene transfer
	Control (HFD)	43,19	9,07	11	IL-18 (HFD)	50,23	4,39	14	%	
Jia et al., 2023	Vehicle	8,49	0,59	6	IL-1β	22,70	3,65	6	%	Recombinant IL-1β
Orecchioni et al., 2022	Vehicle	781700	488500	11	Oct	1305000	463400	10	μm^2	NLRP3 inflammasome activation
	Vehicle	319800	120700	10	Oct	371600	181200	10	μm^2	
Tenger et al., 2005	PBS	15131	6630	4	IL-18	43384	20042	8	μm^2	Recombinant mouse IL-18
Tous et al., 2006	Control	290314	108049	4	rIL-6	115689	29326	8	μm^2	Recombinant mouse IL-6
Whitman et al., 2002	Saline	50642	39576	10	IL-18	112399	41827	10	μm^2	Recombinant IL-18 inhibitor (in different mouse models)
	Saline	23558	35206	8	IL-18	11657	12206	9	μm^2	
Xie et al., 2021	A-control	102326	34551	9	Hhcy	290365	33223	9	μm^2	Sulphur-containing amino acid: IL-1β stimulation

Supplementary Table 8. Sex subgroup meta-analysis decision for cytokine signaling target groups. Number (N) of studies and comparisons performed in males and females and whether a sex subgroup meta-analysis (MA) is performed for every target group, including inhibition of all targets (inhibition total) and stimulation of all targets (stimulation total).

Cytokine signaling target	N studies males	N studies females	N comparisons males	N comparisons females	MA sex subgroup males	MA sex subgroup females
IL-1α inhibition direct	3	0	4	0	No	No
IL-1α inhibition indirect	0	0	0	0	-	-
IL-1α stimulation direct	0	0	0	0	-	-
IL-1α stimulation indirect	0	0	0	0	-	-
IL-1β inhibition direct	5	1	9	1	No	No
IL-1β inhibition indirect	12	2	15	3	Yes	No
IL-1β stimulation direct	1	0	1	0	No	No
IL-1β stimulation indirect	2	0	2	0	No	No
IL-1R inhibition direct	5	4	7	6	No	No
IL-1R inhibition indirect	0	0	0	0	-	-
IL-1R stimulation direct	0	0	0	0	-	-
IL-1R stimulation indirect	0	0	0	0	-	-
IL-18 inhibition direct	1	0	1	0	No	No
IL-18 inhibition indirect	12	2	15	3	Yes	No
IL-18 stimulation direct	3	1	5	1	No	No
IL-18 stimulation indirect	1	0	1	0	No	No
IL-6 inhibition direct	1	0	3	0	No	No
IL-6 inhibition indirect	2	0	2	0	No	No
IL-6 stimulation direct	1	0	1	0	No	No
IL-6 stimulation indirect	0	0	0	0	-	-
IL-6R inhibition direct	1	0	1	0	No	No
IL-6R inhibition indirect	0	0	0	0	-	-
IL-6R stimulation direct	0	0	0	0	-	-
IL-6R stimulation indirect	0	0	0	0	-	-
Inhibition total	28	7	42	10	Yes	No
Stimulation total	7	1	9	1	No	No