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Circulating cytokines and risk of developing hypertension: a systematic review and meta-analysis

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Abstract

Background: Immune responses play a significant role in hypertension, though the importance of key inflammatory mediators remains to be defined. We used a systematic literature review and meta-analysis to study the associations between key cytokines and incident hypertension.

Methods: We performed a systematic search of Pubmed/Medline, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL), for peer-

reviewed studies published up to August 2022. Incident hypertension was defined as systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg and/or the use of antihypertensive medications. Random effects meta-analyses were used to calculate pooled hazard ratios (HRs)/risk ratios (RRs) and 95% confidence intervals by cytokine levels (highest vs. lowest quartile).

Results: Only IL-6 and IL-1β levels have evidence allowing for quantitative evaluation concerning the onset of hypertension. Six studies (10,406 participants, 2,932 incident cases) examined the association of IL-6 with incident hypertension. The highest versus lowest quartile of circulating IL-6 was associated with a significant HR/RR of hypertension (1.61, 95% CI: 1.00 to 2.60; I^2=87%). After adjusting for potential confounders, including body mass index (BMI), HR/RR was no longer significant (HR/RR: 1.24; 95% CI, 0.96 to 1.61; I^2= 56%). About IL-1β, neither the crude (HR/RR: 1.03; 95% CI, 0.60 to 1.76; n=2) nor multivariate analysis (HR/RR: 0.97, 95% CI, 0.60 to 1.56; n=2) suggested a significant association with the risk of developing hypertension.

Conclusions: A limited number of studies suggest that higher IL-6, but not IL-1β, might be associated with the development of hypertension.

Keywords: Cytokines; Incident hypertension; Risk; Systematic review; Meta-analysis

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Nonstandard Abbreviations and Acronyms

ACEIs angiotensin-converting enzyme inhibitors

ARBs angiotensin receptor blockers

ART antiretroviral therapy

BMI body mass index

CENTRAL Cochrane Central Register of Controlled Trials

CIs confidence intervals

CVDs cardiovascular diseases

DBP diastolic blood pressure

ELISA enzyme-linked immunosorbent assay

HIV Human Immunodeficiency Virus

HK Hartung and Knapp

HRs hazard ratios

IL interleukin

MeSH Medical Subject Headings

MESA Multi-Ethnic Study of Atherosclerosis

OR odds ratio

ROBINS-E risk of bias in non-randomized studies of exposures

RRs risk ratios

SNPs three single nucleotide polymorphisms

SBP systolic blood pressure

START Strategic Timing of AntiRetroviral Treatment

TGF-β1 transforming growth factor beta1

TNF-α tumor necrosis factor-alpha

WHI-OS Women's Health Initiative-Observational Study

WESDR Wisconsin Epidemiological Study of Diabetic Retinopathy

1. Introduction

Hypertension is a major modifiable risk factor for cardiovascular diseases (CVDs) but is frequently undiagnosed and poorly controlled[1-3]. The pathophysiology of hypertension is complex[4-9]. Experimental and clinical studies suggest a positive association between pro-inflammatory cytokines and systolic blood pressure (SBP)[10-19]. Consistent with this notion, inhibitors of tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 have been shown to reduce blood pressure in experimental models[7, 20], but findings were contradictory in humans[21-23]. The use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) might suppress the production of IL-6, IL-1β, and TNF-α by various cells, perhaps as a result of their antihypertensive properties[24-26]. The activation of the renin-angiotensin system and

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sympathetic nervous system stimulates the synthesis of proinflammatory cytokines[27-31], which further supports a potential role for cytokines in the regulation of blood pressure. An imbalance between pro-inflammatory cytokines, for instance, TNF-α, IL-6, and IL-1β[32], that initiate inflammation in response to tissue injury, and anti-inflammatory cytokines like interleukin-10 (IL-10), that inhibit excessive inflammatory reactions[33], might lead to the development of hypertension and other severe cardiovascular complications, including coronary artery disease and heart failure[34]. Importantly, recently pharmacological targeting of IL-1β was shown to significantly reduce the rate of secondary cardiovascular events in atherosclerotic patients[35]. Similarly, the effect of IL-6 inhibition in patients at high atherosclerotic risk is currently under investigation[36].

However, whether cytokine levels are associated with the development of hypertension is unclear[37-40]; thus, we performed this systematic review of the literature and a meta-analysis to investigate this association.

2. Methods

This study was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prisma-statement.org/). The review protocol was registered in PROSPERO, the International Prospective Register of Systematic Reviews (crd.york.ac.uk/prospero/index.asp, identifier: CRD42022378211).

2.1. Data Sources and Search Strategy

EC, MS, AOMR and MIM searched MEDLINE (Pubmed), Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL) and Embase 1947-present (Ovid) databases for relevant studies published from database inception to the 23rd of August 2022, using the Medical Subject Headings (MeSH) terms/Emtree and

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keywords related to the topic of interest limited to title and/or abstract. The search was reviewed by an experienced librarian of the University of Glasgow, Paul Cannon. The detailed search strategy for each data item is available in the Supplemental Material.

2.2. Eligibility

We selected studies that reported associations for circulating cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-33, IL-34, IL-35, IL-36, IL-37, IL-38, IL-39, IL-40, TNF-α, TNF-β, TNF-C, IFN-α, IFN-β, IFN- γ, TGF-β, M-CSF, GM-CSF, G-CSF, GDF-15) with incident hypertension in the general population with no restrictions on age, gender, or ethnicity. We included randomized trials and observational studies (cohort studies, nested case–control studies). We excluded studies that enrolled pregnant women with preeclampsia and articles not written in English. Conference abstracts, editorials, letters, comments, cellular and animal model experiments, narrative or systematic reviews and meta-analyses, and ongoing studies were also excluded.

2.3. Definition of Primary and Secondary Outcomes

The primary outcome was the risk for incident hypertension, defined as SBP ≥140mmHg or diastolic blood pressure (DBP) ≥90mmHg and/or the use of antihypertensive medications. The secondary outcomes were the identification of cytokines associated with incident hypertension, and differences in baseline and longitudinal changes in cytokine levels in patients who developed hypertension compared to those who did not.

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2.4. Study Selection

Articles were initially screened by title and abstract according to the inclusion and exclusion criteria, independently by four investigators (EC, MS, AOMR and MIM). For secondary screening, full-text articles and supplemental materials were independently reviewed by four authors (EC, MS, AOMR and MIM). Reasons for study exclusion were recorded and cross-checked. Any inconsistencies were resolved through consultation with a fifth author (TG). A flow diagram summarizes the process of study selection (Figure 1).

2.5. Data Extraction and Quality Assessment

For eligible studies, the following information were independently extracted by three review authors (EC, MS, AOMR): publication data including the first author's name, country, study design, population type, total number of participants, patients with events, follow-up time, incident hypertension definition, baseline and follow-up cytokine levels, change in blood pressure by cytokine levels, participants' baseline demographics [age, gender, ethnicity, body mass index (BMI), glucose, blood lipid levels, blood pressure status, alcohol and tobacco consumption, baseline comorbidities].

Three review authors (EC, AOMR, MIM) independently assessed the risk of bias using the risk of bias in non-randomized studies of exposures (ROBINS-E).

2.6. Statistical Analysis

Pooled estimates of hazard ratios (HRs) and risk ratios (RRs) with 95% confidence intervals (CIs) for incident hypertension were calculated using the DerSimonian and Laird method in a random-effects model for the highest quartile compared with the lowest quartile (reference group) before and after adjustment for potential confounding factors including age, gender, and BMI. When data were available only in figures, HRs

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and RRs were extracted from figures with Digitizelt (version 2.5) software. To account for the small number of studies included, the Hartung and Knapp (HK) correction was used. Cytokine concentrations were reported using the median (interquartile range, IQR) or mean differences and 95% CI. Heterogeneity among the studies included in the meta-analysis was assessed through visual inspection of the forest plots and using the I^2 statistic. All analysis was performed using the R package meta, Version 5.2 with two-sided $p < 0.05$ set for statistical significance.

3. Results

A total of 725 studies were identified through the initial search of the databases. Of these, 156 studies were duplicates. Title and abstract screening identified 39 studies for final full-text review using the inclusion/exclusion criteria. However, after further analysis of the full text of these articles, 24 were excluded because they did not report the outcome or the population of interest. Finally, the search yielded 15 studies for the qualitative analysis and of these, 6 studies were included in the quantitative analysis. The process of literature selection is shown in Figure 1. Among the searched cytokines, a pooled estimate of HRs and RRs for incident hypertension could only be produced for IL-6 and IL-1β that were thus subject to the meta-analysis, while other cytokines are further discussed in the qualitative context.

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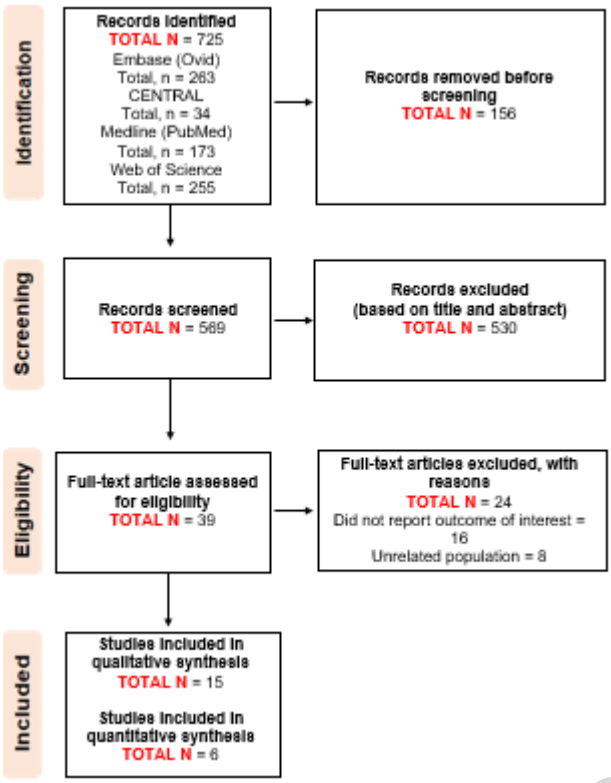

Figure 1. Flow chart reporting the search strategy according to PRISMA.

3.1 Characteristics of the Studies and Quality Assessment

Of the six studies included in the meta-analysis, three were based on populations originally enrolled in randomized trials. The first study by Sesso (2007)[40] was a prospective nested case-control analysis from the Women's Health Study, a randomized trial assessing the role of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer, the other (2015)[41] was a prospective nested case-control analysis of the Physicians' Health Study, a randomized trial of low-dose aspirin and beta carotene in the primary prevention of CVD and cancer. The study by Ghazi and colleagues[38] was a prospective cohort analysis from the Strategic Timing of AntiRetroviral Treatment (START) trial assessing immediate vs. deferred antiretroviral therapy (ART) in Human Immunodeficiency Virus (HIV)-positive participants. Wang and colleagues[42] reported findings from a nested-control analysis of the Women's

Health Initiative-Observational Study (WHI-OS); the remaining two were observational, prospective cohort studies[39, 43]. Four studies were conducted only in the USA[39-42], one in South Africa[43], and one was from USA, Asia, Africa, Australia, Europe, Israel and Latin America[38]. The population included in the meta-analysis varied among the six studies. One study reported results for middle-aged and older women[40], one reported separate analyses for black and white postmenopausal women[42], and one reported results for middle-aged and older men[41]. Crouch and colleagues reported separate results for young black and white men and women[43]; upon request, we obtained the original data[44] of this study and calculated the hazard ratio for the highest quartile compared with the lowest quartile of IL-6 and IL-1β, before and after adjustment for age, sex and BMI. Ghazi et al. reported results for HIV-positive persons[38]. Lakoski and colleagues reported results from a longitudinal analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) study including the adult general population[39].

A total of six studies with 10,406 participants aged 20-84 years and 2,932 incident cases of hypertension were included in the meta-analysis. The total follow-up times ranged from 3 to 14 years and the confounder factors more commonly used for adjustment were age, BMI, smoking status and alcohol use; specifically, all the studies controlled for age, smoking, BMI and alcohol intake, three controlled for gender and ethnicity[38, 39, 43]. Circulating cytokine levels of IL-6 were measured by ultrasensitive enzyme-linked immunosorbent assay (ELISA)[38-42] or Luminex xMAP technology[43] in serum or plasma samples. All studies defined incident hypertension as new-onset hypertension (SBP/DBP ≥140/90 mm Hg) or use of antihypertensive medications. The main characteristics of studies included in the current meta-analysis and patients' characteristics of studies included in the meta-analysis are reported in the supplemental material (Table S1 and Table S2).

Most of the studies were assessed at low risk of bias, some concerns were reported about two studies due to self-reports of BMI values[40, 41] and about one study for 11% missing data on IL-1β[42]; all studies were included in the meta-analysis. The result of the risk of bias assessment through ROBINS-E is shown in Supplemental Material (Table S3).

3.2. Interleukin-6

All studies included in the quantitative analysis reported effect estimates per quartile of IL-6 levels. In crude models, the highest quartile of IL-6 levels was associated with a significantly higher risk of developing hypertension than the lowest quartile, with substantial heterogeneity across studies (Figure 2A; HR/RR: 1.61; [95% CI, 1.00 to 2.60]; I^2=87%; n= 6]. In multivariable models not adjusted for BMI, HR/RR for the highest versus the lowest quartile of IL-6 was still significantly associated greater with the risk of hypertension (Figure 2B; HR/RR: 1.71; [95% CI, 1.22 to 2.39]; I^2=39%; n= 5). There was no significant association after adjustment including BMI (Figure 2C; HR/RR: 1.24; 95% CI, 0.96 to 1.61; I^2= 56%, n= 6). In sensitivity analysis, when we excluded adults with HIV[38], the highest quartiles of IL-6 were associated with risk of developing hypertension in both crude and models adjusted for BMI (Figure S1; respectively A, HR/RR: 1.78; [95% CI, 1.04 to 3.04]; I^2=79%; n= 5; B, HR/RR: 1.41; [95% CI, 1.19 to 1.67]; I^2=0%; n= 5).

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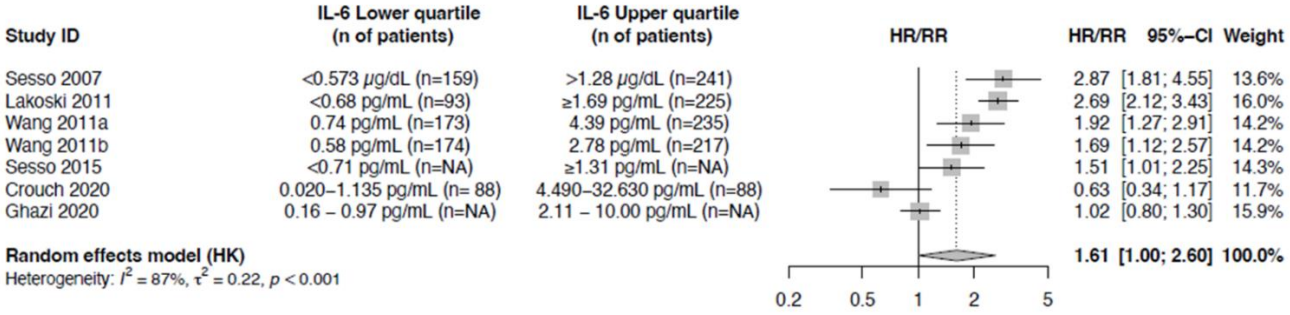

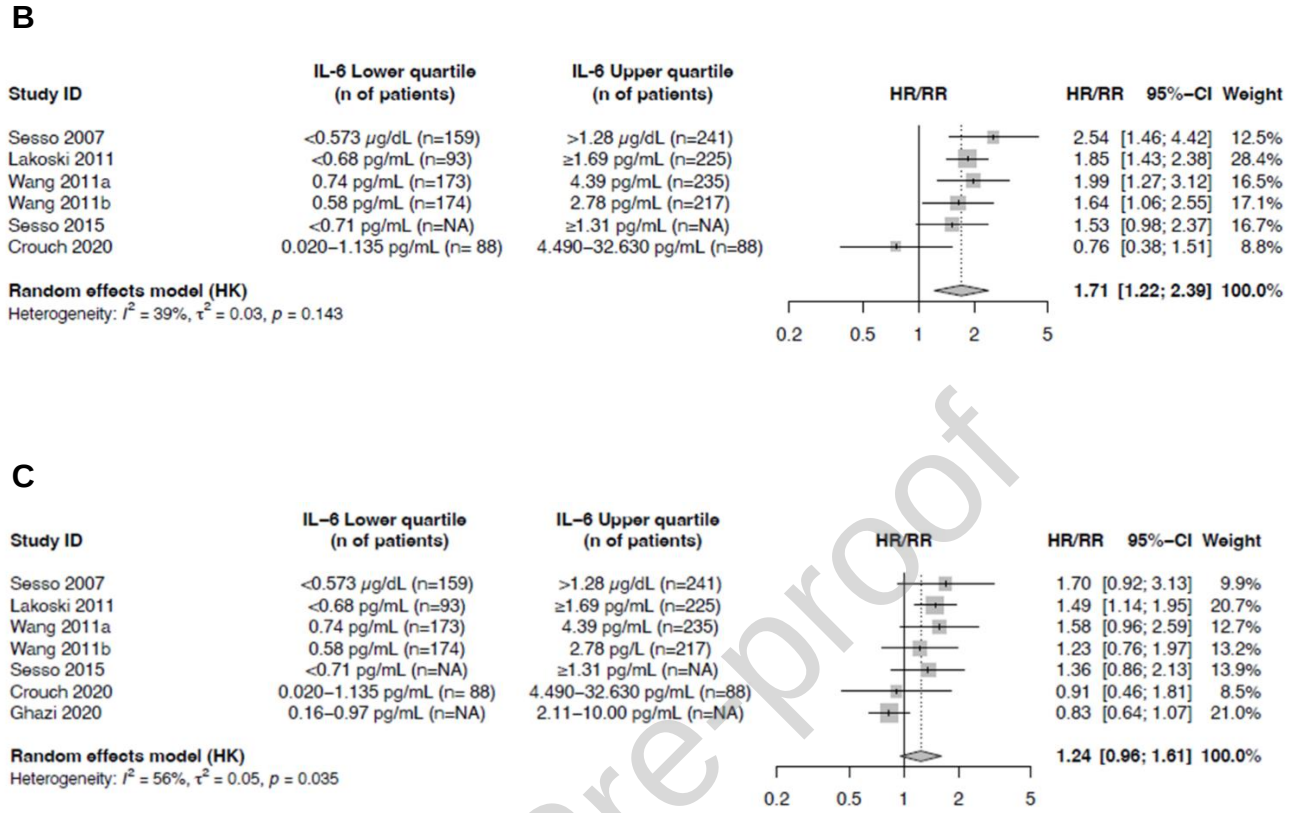

Figure 2. Forest plots of pooled HR/RR of hypertension for the highest versus lowest quartile of IL-6. Hazard ratio (HR)/Risk ratio (RR) and 95% confidence interval (CI) from the eligible studies of the association between IL-6 circulating levels and incident hypertension estimates in a random effects model with crude RR/HR pooled in (A), adjusted RR/HR pooled in (B) without BMI and adjusted RR/HR pooled in (C) including BMI.

3.3. Interleukin-1β

Two studies assessed the risk of new-onset hypertension associated with higher quartiles of IL-1β[42, 43]. In crude models, HR/RR comparing the highest versus the lowest quartile of IL-1β was 1.03 [95% CI, 0.60 to 1.76]; I^2= 0%; n=2; there was non-significant difference in multivariable models adjusted, or not, for BMI (respectively

HR/RR: 1.02; [95% CI, 0.54 to 1.92], I^2= 0%; n= 2; HR/RR: 0.97; [95% CI, 0.60 to 1.56]; I^2= 0%; n= 2).

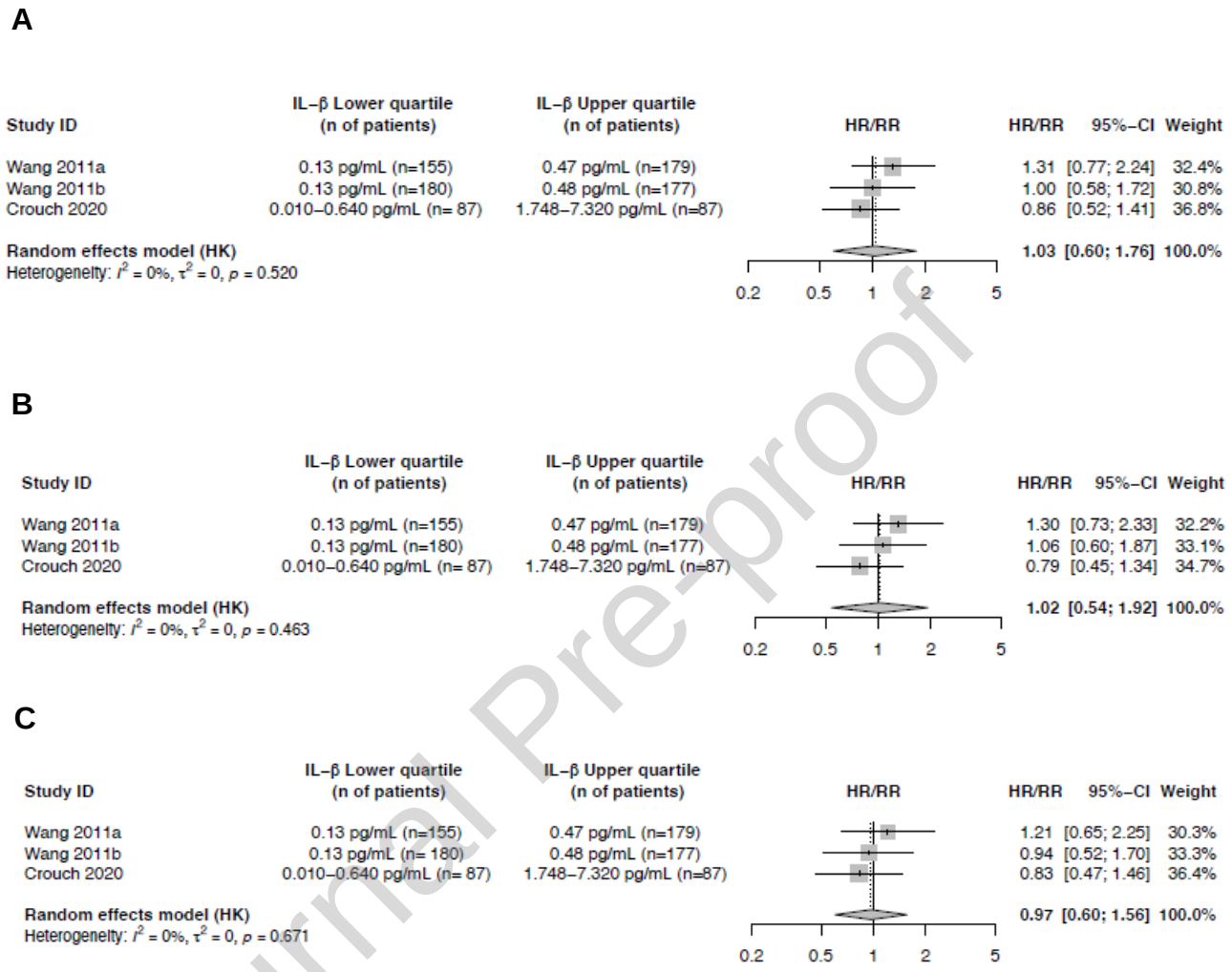

Figure 3. Forest plots of pooled HR/RR of hypertension for the highest versus lowest quartile of IL-1β. Hazard ratio (HR)/Risk ratio (RR) and 95% confidence interval (CI) from the eligible studies of the association between IL-1β circulating levels and incident hypertension estimates in a random effects model with crude RR/HR pooled in (A), adjusted RR/HR pooled in (B) without BMI and adjusted RR/HR pooled in (C) including BMI.

3.4. Other cytokines

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It has been shown that high levels of plasma transforming growth factor β1 (TGF-β1) predict the development of hypertension[45]. Specifically, TGF-β1 was significantly related to higher odds of developing incident hypertension in a Japanese normotensive population (OR 1.948; [95% CI, 1.015 to 3.740]; P = 0.045).

In a study that enrolled patients with type 1 diabetes mellitus (Wisconsin Epidemiological Study of Diabetic Retinopathy; WESDR)[46] followed up for over 15 years, serum IL-6 and TNF-α were associated with the development of hypertension in models adjusted for age and sex; however, when BMI was added to the model only soluble intercellular adhesion molecule-1 (sICAM-1) was associated with greater risk. In a cohort of 471 postmenopausal women, of whom 195 developed hypertension, no statistically significant associations were found amongst several markers, including IL-8, IL-10, TNF-α, IL-2, IL-4 and IL-6 with greater risk[47]. These studies did not report RRs/HRs according to the highest quartile compared with the lowest quartile of the cytokines, therefore were not included in our quantitative analysis.

3.5. Baseline and follow-up plasma and serum cytokine levels

It has been reported inconsistent evidence of statistically significant differences in baseline IL-6 levels among subjects who developed hypertension compared to those who did not[38-42, 47-50].

Regarding IL-1β, Mauno and colleagues showed that high levels of baseline IL-1β were significantly higher for subjects who developed hypertension compared to subjects without incident hypertension[51]. Similarly, in a nested case-control study of 363 healthy subjects aged 20 to 69 years, IL-1β, but not TNF-α and IL-6, was higher in subjects who developed hypertension than those who did not at both baseline (P = 0.028, adjusted for BMI) and follow-up (P = 0.003, adjusted for BMI)[50]. Baseline cytokine levels in plasma or serum and their follow-up changes are shown in Supplemental Material (Table S4).

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4. Discussion

In this systematic review and meta-analysis, we found that higher levels of IL-6 might be associated with a greater, but not robust (lower 95% CI = 1.0) risk of developing hypertension. In contrast, higher levels of IL-1β were not associated with the risk of incident hypertension. There was insufficient evidence for other cytokines.

IL-6 is a pleiotropic cytokine secreted by various cells including macrophages, monocytes, T lymphocytes, endothelial cells and vascular smooth muscle cells, typically regarded as a pro-inflammatory cytokine and an anti-inflammatory myokine[52]. Preclinical evidence suggests that IL-6 might be involved in the initiation, as well as in the progression and maintenance of hypertension through a reduction in nitric oxide bioavailability, increase in vascular superoxide, regulation of angiotensin II expression and alterations in vascular function and structure[53, 54]. In line with a previous meta-analysis[55] that included a smaller number of studies, we found that the positive association between IL-6 and risk of hypertension became insignificant after adjustment for BMI. This finding suggests a link between IL-6 and obesity driving hypertension risk. Obesity is a well-known risk factor for hypertension, and weight loss is an important treatment strategy to prevent and control hypertension[56-58]. A positive relationship between BMI and circulating IL-6 has been shown in postmenopausal women[59] as well as in healthy subjects with obesity[60]. It has been estimated that around 25% of circulating IL-6 is released by subcutaneous adipose tissue[61, 62]; thus, adipose tissue-derived IL-6 may be involved in hypertension development.

Obesity, inflammation and hypertension share common underlying cellular and humoral mechanisms involving oxidative stress[63, 64], activation of cytokines and activation of the renin–angiotensin system[65], and alteration of immune function. In our sensitivity analysis, removing patients with HIV[38], high baseline IL-6 levels were

significantly related to a higher risk of developing incident hypertension in both crude and adjusted models after adjustment for BMI suggesting IL-6 as independent from BMI in predicting hypertension incidence in individuals without HIV. Hypertension is a growing problem in HIV-infected adults, especially in HIV-infected adults on antiretroviral therapy (ART)[66-71]. However, there is no consensus about the association between high levels of IL-6 as a predictor of incident hypertension in HIV-infected adults[72, 73], highlighting the need for a better understanding of this relationship in HIV population. On the other hand, IL-6 has been shown to predict cardiovascular mortality in black South Africans also when adjusting for BMI[74], therefore may be interesting investigating more in-depth the association of cytokines with the risk of developing hypertension and adiposity in black and white individuals. Pharmacological targeting of IL-6 is currently under investigation in people with CVDs (ClinicalTrials.gov Identifier: NCT05021835)[36]. Future studies examining the effect of IL-6 inhibition on vascular and renal inflammation and function in hypertension are therefore required.

The mechanisms underlying the involvement of cytokines in hypertension range from classical immune-regulatory functions[75] to direct modulation of vascular and renal functions[76]. The importance of these observations extends beyond our understating of the pathophysiology of hypertension and provides important clues for common mechanisms between hypertension, atherosclerosis[77] and heart failure[78]. It is also important to consider inflammatory cytokines as biomarkers for identifying patients presenting with the immune and inflammatory mechanisms of hypertension[79] and atherosclerosis[80].

Our meta-analysis has several strengths. First, we performed a broad and systematic search to identify cytokines associated with incident hypertension. Secondly, our study

shows that the association between IL-6 and the risk of hypertension is weakened by BMI, highlighting the important relationship between inflammation and adiposity in the risk of developing hypertension. Third, we have updated the existing evidence of the role of elevated IL-6 on the risk of hypertension with a robust sample size, inclusion of modern cohorts and unpublished data.

There are also several limitations in this study. First, cytokines were only measured at enrollment. Second, the number of studies for IL-1β analysis was limited to two. Third, even if we reported multivariate analysis after adjustment for known risk factors, residual confounding may occur. Fourth, we were unable to perform subgroup analysis based on characteristics, such as race/ethnicity or genetic polymorphisms, that may predispose to hypertension.

5. Conclusions

Higher levels of circulating IL-6 concentrations are significantly associated with risk of incident hypertension, whereas IL-1β levels are not. After adjusting for BMI, the correlation between IL-6 and hypertension risk is not statistically significant. This underscores the relationship between inflammation and adiposity in hypertension onset. Further studies are needed to elucidate links between immune cytokine signature to incident hypertension.

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Disclosures

TJG reports consulting fees for Moderna. All the other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Collaboration NCDRF. Worldwide trends in blood pressure from 1975 to 2015: A pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet*. 2017;389:37-55
2. Liberale L, Montecucco F, Schwarz L, Luscher TF, Camici GG. Inflammation and cardiovascular diseases: Lessons from seminal clinical trials. *Cardiovasc Res*. 2021;117:411-422
3. Cheema KM, Dicks E, Pearson J, Samani NJ. Long-term trends in the epidemiology of cardiovascular diseases in the uk: Insights from the british heart foundation statistical compendium. *Cardiovasc Res*. 2022;118:2267-2280
4. Nosalski R, McGinnigle E, Siedlinski M, Guzik TJ. Novel immune mechanisms in hypertension and cardiovascular risk. *Curr Cardiovasc Risk Rep*. 2017;11:12
5. Griendling KK, Camargo LL, Rios FJ, Alves-Lopes R, Montezano AC, Touyz RM. Oxidative stress and hypertension. *Circ Res*. 2021;128:993-1020
6. Brandes RP. Endothelial dysfunction and hypertension. *Hypertension*. 2014;64:924-928
7. Murray EC, Nosalski R, MacRitchie N, Tomaszewski M, Maffia P, Harrison DG, et al. Therapeutic targeting of inflammation in hypertension: From novel mechanisms to translational perspective. *Cardiovasc Res*. 2021;117:2589-2609
8. Siedlinski M, Jozefczuk E, Xu X, Teumer A, Evangelou E, Schnabel RB, et al. White blood cells and blood pressure: A mendelian randomization study. *Circulation*. 2020;141:1307-1317

9. Mikolajczyk TP, Szczepaniak P, Vidler F, Maffia P, Graham GJ, Guzik TJ. Role of inflammatory chemokines in hypertension. *Pharmacology & therapeutics*. 2021;223:107799
10. Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. *Hypertension*. 2001;38:399-403
11. Nguyen H, Chiasson VL, Chatterjee P, Kopriva SE, Young KJ, Mitchell BM. Interleukin-17 causes rho-kinase-mediated endothelial dysfunction and hypertension. *Cardiovasc Res*. 2013;97:696-704
12. Dalekos GN, Elisaf M, Bairaktari E, Tsolas O, Siamopoulos KC. Increased serum levels of interleukin-1beta in the systemic circulation of patients with essential hypertension: Additional risk factor for atherogenesis in hypertensive patients? *J Lab Clin Med*. 1997;129:300-308
13. Chamarthi B, Williams GH, Ricchiuti V, Srikumar N, Hopkins PN, Luther JM, et al. Inflammation and hypertension: The interplay of interleukin-6, dietary sodium, and the renin-angiotensin system in humans. *Am J Hypertens*. 2011;24:1143-1148
14. Elmarakby AA, Quigley JE, Imig JD, Pollock JS, Pollock DM. Tnf-alpha inhibition reduces renal injury in doca-salt hypertensive rats. *Am J Physiol Regul Integr Comp Physiol*. 2008;294:R76-83
15. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik TJ, et al. Interleukin 17 promotes angiotensin ii-induced hypertension and vascular dysfunction. *Hypertension*. 2010;55:500-507
16. Saleh MA, McMaster WG, Wu J, Norlander AE, Funt SA, Thabet SR, et al. Lymphocyte adaptor protein lnk deficiency exacerbates hypertension and end-organ inflammation. *J Clin Invest*. 2015;125:1189-1202
17. Crosswhite P, Sun Z. Ribonucleic acid interference knockdown of interleukin 6 attenuates cold-induced hypertension. *Hypertension*. 2010;55:1484-1491
18. Lee DL, Sturgis LC, Labazi H, Osborne JB, Jr., Fleming C, Pollock JS, et al. Angiotensin ii hypertension is attenuated in interleukin-6 knockout mice. *Am J Physiol Heart Circ Physiol*. 2006;290:H935-940
19. Gonzalez-Amor M, Garcia-Redondo AB, Jorge I, Zalba G, Becares M, Ruiz-Rodriguez MJ, et al. Interferon-stimulated gene 15 pathway is a novel mediator of endothelial dysfunction and aneurysms development in angiotensin ii infused mice through increased oxidative stress. *Cardiovasc Res*. 2022;118:3250-3268
20. Abdelrahman AM, Al Suleimani YM, Ashique M, Manoj P, Ali BH. Effect of infliximab and tocilizumab on fructose-induced hyperinsulinemia and hypertension in rats. *Biomed Pharmacother*. 2018;105:182-186
21. Faria AP, Ritter AMV, Santa-Catharina A, Souza DP, Naseri EP, Bertolo MB, et al. Effects of anti-tnf alpha therapy on blood pressure in resistant hypertensive subjects: A randomized, double-blind, placebo-controlled pilot study. *Arq Bras Cardiol*. 2021;116:443-451
22. Rothman AM, MacFadyen J, Thuren T, Webb A, Harrison DG, Guzik TJ, et al. Effects of interleukin-1beta inhibition on blood pressure, incident hypertension, and residual inflammatory risk: A secondary analysis of cantos. *Hypertension*. 2020;75:477-482
23. Provan SA, Berg IJ, Hammer HB, Mathiessen A, Kvien TK, Semb AG. The impact of newer biological disease modifying anti-rheumatic drugs on cardiovascular risk factors: A 12-month longitudinal study in rheumatoid arthritis patients treated with rituximab, abatacept and tociliziumab. *PLoS One*. 2015;10:e0130709

24. Schindler R, Dinarello CA, Koch KM. Angiotensin-converting-enzyme inhibitors suppress synthesis of tumour necrosis factor and interleukin 1 by human peripheral blood mononuclear cells. *Cytokine*. 1995;7:526-533
25. Peeters AC, Netea MG, Kullberg BJ, Thien T, van der Meer JW. The effect of renin-angiotensin system inhibitors on pro- and anti-inflammatory cytokine production. *Immunology*. 1998;94:376-379
26. Vazquez-Oliva G, Fernandez-Real JM, Zamora A, Vilaseca M, Badimon L. Lowering of blood pressure leads to decreased circulating interleukin-6 in hypertensive subjects. *J Hum Hypertens*. 2005;19:457-462
27. Zhang ZH, Wei SG, Francis J, Felder RB. Cardiovascular and renal sympathetic activation by blood-borne tnf-alpha in rat: The role of central prostaglandins. *Am J Physiol Regul Integr Comp Physiol*. 2003;284:R916-927
28. Funakoshi Y, Ichiki T, Ito K, Takeshita A. Induction of interleukin-6 expression by angiotensin ii in rat vascular smooth muscle cells. *Hypertension*. 1999;34:118-125
29. Han Y, Runge MS, Brasier AR. Angiotensin ii induces interleukin-6 transcription in vascular smooth muscle cells through pleiotropic activation of nuclear factor-kappa b transcription factors. *Circ Res*. 1999;84:695-703
30. Ruiz-Ortega M, Ruperez M, Lorenzo O, Esteban V, Blanco J, Mezzano S, et al. Angiotensin ii regulates the synthesis of proinflammatory cytokines and chemokines in the kidney. *Kidney Int Suppl*. 2002:S12-22
31. Sanz-Rosa D, Oubina MP, Cediel E, de Las Heras N, Vegazo O, Jimenez J, et al. Effect of at1 receptor antagonism on vascular and circulating inflammatory mediators in shr: Role of nf-kappab/ikappab system. *Am J Physiol Heart Circ Physiol*. 2005;288:H111-115
32. Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease. *Int J Mol Sci*. 2019;20
33. Opal SM, DePalo VA. Anti-inflammatory cytokines. *Chest*. 2000;117:1162-1172
34. Caiazzo E, Rezig AOM, Bruzzese D, Ialenti A, Cicala C, Cleland JGF, et al. Systemic administration of glucocorticoids, cardiovascular complications and mortality in patients hospitalised with covid-19, sars, mers or influenza: A systematic review and meta-analysis of randomised trials. *Pharmacol Res*. 2022;176:106053
35. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *The New England journal of medicine*. 2017;377:1119-1131
36. Ridker PM. From rescue to zeus: Will interleukin-6 inhibition with ziltivekimab prove effective for cardiovascular event reduction? *Cardiovascular research*. 2021;117:e138-e140
37. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (c-reactive protein, interleukin-6, and tnf-alpha) and essential hypertension. *J Hum Hypertens*. 2005;19:149-154
38. Ghazi L, Baker JV, Sharma S, Jain MK, Palfreeman A, Necsoi C, et al. Role of inflammatory biomarkers in the prevalence and incidence of hypertension among hiv-positive participants in the start trial. *Am J Hypertens*. 2020;33:43-52
39. Lakoski SG, Cushman M, Siscovick DS, Blumenthal RS, Palmas W, Burke G, et al. The relationship between inflammation, obesity and risk for hypertension in the multi-ethnic study of atherosclerosis (mesa). *J Hum Hypertens*. 2011;25:73-79

40. Sesso HD, Wang L, Buring JE, Ridker PM, Gaziano JM. Comparison of interleukin-6 and c-reactive protein for the risk of developing hypertension in women. *Hypertension*. 2007;49:304-310
41. Sesso HD, Jimenez MC, Wang L, Ridker PM, Buring JE, Gaziano JM. Plasma inflammatory markers and the risk of developing hypertension in men. *J Am Heart Assoc*. 2015;4:e001802
42. Wang L, Manson JE, Gaziano JM, Liu S, Cochrane B, Cook NR, et al. Circulating inflammatory and endothelial markers and risk of hypertension in white and black postmenopausal women. *Clin Chem*. 2011;57:729-736
43. Crouch SH, Botha-Le Roux S, Delles C, Graham LA, Schutte AE. Inflammation and hypertension development: A longitudinal analysis of the african-predict study. *Int J Cardiol Hypertens*. 2020;7:100067
44. Schutte AE, Gona PN, Delles C, Uys AS, Burger A, Mels CM, et al. The african prospective study on the early detection and identification of cardiovascular disease and hypertension (african-predict): Design, recruitment and initial examination. *Eur J Prev Cardiol*. 2019;26:458-470
45. Nakao E, Adachi H, Enomoto M, Fukami A, Kumagai E, Nakamura S, et al. Elevated plasma transforming growth factor beta1 levels predict the development of hypertension in normotensives: The 14-year follow-up study. *Am J Hypertens*. 2017;30:808-814
46. Sahakyan K, Klein BE, Myers CE, Tsai MY, Klein R. Novel risk factors in long-term hypertension incidence in type 1 diabetes mellitus. *Am Heart J*. 2010;159:1074-1080
47. Gordon JH, LaMonte MJ, Zhao J, Genco RJ, Cimato TR, Hovey KM, et al. The association between serum inflammatory biomarkers and incident hypertension among postmenopausal women in the buffalo osteoperio study. *J Hum Hypertens*. 2021;35:791-799
48. Cheung BM, Ong KL, Tso AW, Leung RY, Cherny SS, Sham PC, et al. Relationship of plasma interleukin-6 and its genetic variants with hypertension in hong kong chinese. *Am J Hypertens*. 2011;24:1331-1337
49. Pavuk M, Serio TC, Cusack C, Cave M, Rosenbaum PF, Birnbaum LS. Hypertension in relation to dioxins and polychlorinated biphenyls from the anniston community health survey follow-up. *Environ Health Perspect*. 2019;127:127007
50. Yoo HJ, Kim M, Lee SH, Lee JH. Elevated lipoprotein-associated phospholipase a(2) independently affects age-related increases in systolic blood pressure: A nested case-control study in a prospective korean cohort. *Int J Hypertens*. 2020;2020:5693271
51. Mauno V, Hannu K, Esko K. Proinflammation and hypertension: A population-based study. *Mediators Inflamm*. 2008;2008:619704
52. Barton BE. The biological effects of interleukin 6. *Med Res Rev*. 1996;16:87-109
53. Schrader LI, Kinzenbaw DA, Johnson AW, Faraci FM, Didion SP. Il-6 deficiency protects against angiotensin ii induced endothelial dysfunction and hypertrophy. *Arterioscler Thromb Vasc Biol*. 2007;27:2576-2581
54. Gomolak JR, Didion SP. Angiotensin ii-induced endothelial dysfunction is temporally linked with increases in interleukin-6 and vascular macrophage accumulation. *Front Physiol*. 2014;5:396
55. Jayedi A, Rahimi K, Bautista LE, Nazarzadeh M, Zargar MS, Shab-Bidar S. Inflammation markers and risk of developing hypertension: A meta-analysis of cohort studies. *Heart*. 2019;105:686-692

56. Kuwabara M, Kuwabara R, Niwa K, Hisatome I, Smits G, Roncal-Jimenez CA, et al. Different risk for hypertension, diabetes, dyslipidemia, and hyperuricemia according to level of body mass index in japanese and american subjects. *Nutrients*. 2018;10
57. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: A meta-analysis of randomized controlled trials. *Hypertension*. 2003;42:878-884
58. Xu X, Eales JM, Jiang X, Sanderson E, Drzal M, Saluja S, et al. Contributions of obesity to kidney health and disease: Insights from mendelian randomization and the human kidney transcriptomics. *Cardiovasc Res*. 2022;118:3151-3161
59. Straub RH, Hense HW, Andus T, Scholmerich J, Riegger GA, Schunkert H. Hormone replacement therapy and interrelation between serum interleukin-6 and body mass index in postmenopausal women: A population-based study. *J Clin Endocrinol Metab*. 2000;85:1340-1344
60. Werida RH, El-Gharbawy NM, Mostafa TM. Circulating il-6, clusterin and irisin in obese subjects with different grades of obesity: Association with insulin resistance and sexual dimorphism. *Arch Endocrinol Metab*. 2021;65:126-136
61. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. *J Clin Endocrinol Metab*. 1997;82:4196-4200
62. Schmidt FM, Weschenfelder J, Sander C, Minkwitz J, Thormann J, Chittka T, et al. Inflammatory cytokines in general and central obesity and modulating effects of physical activity. *PLoS One*. 2015;10:e0121971
63. Camargo LL, Montezano AC, Hussain M, Wang Y, Zou Z, Rios FJ, et al. Central role of c-src in nox5- mediated redox signalling in vascular smooth muscle cells in human hypertension. *Cardiovasc Res*. 2022;118:1359-1373
64. Sagris M, Antonopoulos AS, Theofilis P, Oikonomou E, Siasos G, Tsalamandris S, et al. Risk factors profile of young and older patients with myocardial infarction. *Cardiovasc Res*. 2022;118:2281-2292
65. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress and coronary heart disease: Is interleukin-6 the link? *Atherosclerosis*. 2000;148:209-214
66. Gazzaruso C, Bruno R, Garzaniti A, Giordanetti S, Fratino P, Sacchi P, et al. Hypertension among hiv patients: Prevalence and relationships to insulin resistance and metabolic syndrome. *J Hypertens*. 2003;21:1377-1382
67. Peck RN, Shedafa R, Kalluvya S, Downs JA, Todd J, Suthanthiran M, et al. Hypertension, kidney disease, hiv and antiretroviral therapy among tanzanian adults: A cross-sectional study. *BMC Med*. 2014;12:125
68. Xu Y, Chen X, Wang K. Global prevalence of hypertension among people living with hiv: A systematic review and meta-analysis. *J Am Soc Hypertens*. 2017;11:530-540
69. Nduka CU, Stranges S, Sarki AM, Kimani PK, Uthman OA. Evidence of increased blood pressure and hypertension risk among people living with hiv on antiretroviral therapy: A systematic review with meta-analysis. *J Hum Hypertens*. 2016;30:355-362
70. Onen NF, Overton ET, Seyfried W, Stumm ER, Snell M, Mondy K, et al. Aging and hiv infection: A comparison between older hiv-infected persons and the general population. *HIV Clin Trials*. 2010;11:100-109
71. Fahme SA, Bloomfield GS, Peck R. Hypertension in hiv-infected adults: Novel pathophysiologic mechanisms. *Hypertension*. 2018;72:44-55

72. Batavia AS, Severe P, Lee MH, Apollon A, Zhu YS, Dupnik KM, et al. Blood pressure and mortality in a prospective cohort of hiv-infected adults in port-au-prince, haiti. *J Hypertens*. 2018;36:1533-1539
73. Okello S, Asiimwe SB, Kanyesigye M, Muyindike WR, Boum Y, 2nd, Mwebesa BB, et al. D-dimer levels and traditional risk factors are associated with incident hypertension among hiv-infected individuals initiating antiretroviral therapy in uganda. *J Acquir Immune Defic Syndr*. 2016;73:396-402
74. Botha S, Fourie CMT, Schutte R, Eugen-Olsen J, Pretorius R, Schutte AE. Soluble urokinase plasminogen activator receptor as a prognostic marker of all-cause and cardiovascular mortality in a black population. *Int J Cardiol*. 2015;184:631-636
75. Bullenkamp J, Mengoni V, Kaur S, Chhetri I, Dimou P, Astroulakis ZMJ, et al. Interleukin-7 and interleukin-15 drive cd4+cd28null t lymphocyte expansion and function in patients with acute coronary syndrome. *Cardiovasc Res*. 2021;117:1935-1948
76. Alexander Y, Osto E, Schmidt-Trucksass A, Shechter M, Trifunovic D, Duncker DJ, et al. Endothelial function in cardiovascular medicine: A consensus paper of the european society of cardiology working groups on atherosclerosis and vascular biology, aorta and peripheral vascular diseases, coronary pathophysiology and microcirculation, and thrombosis. *Cardiovasc Res*. 2021;117:29-42
77. Welsh P, Grassia G, Botha S, Sattar N, Maffia P. Targeting inflammation to reduce cardiovascular disease risk: A realistic clinical prospect? *British journal of pharmacology*. 2017;174:3898-3913
78. Pugliese NR, Pellicori P, Filidei F, De Biase N, Maffia P, Guzik TJ, et al. Inflammatory pathways in heart failure with preserved left ventricular ejection fraction: Implications for future interventions. *Cardiovascular research*. 2023;118:3536-3555
79. Evans PC, Davidson SM, Wojta J, Back M, Bollini S, Brittan M, et al. From novel discovery tools and biomarkers to precision medicine-basic cardiovascular science highlights of 2021/22. *Cardiovasc Res*. 2022;118:2754-2767
80. Hettwer J, Hinterdobler J, Miritsch B, Deutsch MA, Li X, Mauersberger C, et al. Interleukin-1beta suppression dampens inflammatory leucocyte production and uptake in atherosclerosis. *Cardiovasc Res*. 2022;118:2778-2791

Declaration of Competing Interest

Tomasz Jan Guzik reports consulting fees for Moderna. All the other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Graphical abstract

Circulating cytokines and risk of developing hypertension: a systematic review and meta-analysis

Data search

Medline (PubMed), Web of Science, Embase (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL) databases

Up to 23rd of August 2022

Participants

n=10,406
aged 20-84 years
6 observational studies

Main outcome

Incident hypertension defined as...

Systolic blood pressure: ≥140mmHg or Diastolic blood pressure: ≥90mmHg

and/or

Use of antihypertensive medications

by circulating cytokines

(IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-33, IL-34, IL-35, IL-36, IL-37, IL-38, IL-39, IL-40, TNF-α, TNF-β, TNF-C, IFN-α, IFN-β, IFN- γ, TGF-β, M-CSF, GM-CSF, G-CSF, GDF-15)

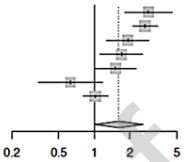
Findings

Among the searched cytokines, a pooled estimate of Hazard and Risk Ratios for incident hypertension could only be produced for IL-6 and IL-1β and was only significant for IL-6

Crude model

Study ID	IL-6 Lower quartile (n of patients)	IL-6 Upper quartile (n of patients)	HR/RR	HR/RR 95%-CI	Weight
Sesso 2007	<0.573 µg/dL (n=159)	>1.28 µg/dL (n=241)		2.87 [1.81; 4.55]	13.6%
Lakoski 2011	<0.68 pg/mL (n=93)	≥1.69 pg/mL (n=225)		2.69 [2.12; 3.43]	16.0%
Wang 2011a	0.74 pg/mL (n=173)	4.39 pg/mL (n=235)		1.92 [1.27; 2.91]	14.2%
Wang 2011b	0.58 pg/mL (n=174)	2.78 pg/mL (n=217)		1.69 [1.12; 2.57]	14.2%
Sesso 2015	<0.71 pg/mL (n=NA)	≥1.31 pg/mL (n=NA)		1.51 [1.01; 2.25]	14.3%
Crouch 2020	0.020–1.135 pg/mL (n= 88)	4.490–32.630 pg/mL (n=88)		0.63 [0.34; 1.17]	11.7%
Ghazi 2020	0.16 – 0.97 pg/mL (n=NA)	2.11 – 10.00 pg/mL (n=NA)		1.02 [0.80; 1.30]	15.9%
Random effects model (HK)				1.61 [1.00; 2.60]	100.0%

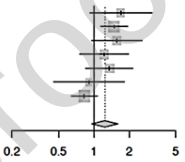
Heterogeneity: I^2 = 87%, τ^2 = 0.22, p < 0.001



Adjusted model including body mass index

Study ID	IL-6 Lower quartile (n of patients)	IL-6 Upper quartile (n of patients)	HR/RR	HR/RR 95%-CI	Weight
Sesso 2007	<0.573 µg/dL (n=159)	>1.28 µg/dL (n=241)		1.70 [0.92; 3.13]	9.9%
Lakoski 2011	<0.68 pg/mL (n=93)	≥1.69 pg/mL (n=225)		1.49 [1.14; 1.95]	20.7%
Wang 2011a	0.74 pg/mL (n=173)	4.39 pg/mL (n=235)		1.58 [0.96; 2.59]	12.7%
Wang 2011b	0.58 pg/mL (n=174)	2.78 pg/L (n=217)		1.23 [0.76; 1.97]	13.2%
Sesso 2015	<0.71 pg/mL (n=NA)	≥1.31 pg/mL (n=NA)		1.36 [0.86; 2.13]	13.9%
Crouch 2020	0.020–1.135 pg/mL (n= 88)	4.490–32.630 pg/mL (n=88)		0.91 [0.46; 1.81]	8.5%
Ghazi 2020	0.16–0.97 pg/mL (n=NA)	2.11–10.00 pg/mL (n=NA)		0.83 [0.64; 1.07]	21.0%
Random effects model (HK)				1.24 [0.96; 1.61]	100.0%

Heterogeneity: I^2 = 56%, τ^2 = 0.05, p = 0.035



Conclusions

Higher levels of circulating IL-6, but not IL-1β, are significantly associated with risk of incident hypertension. After adjusting for body mass index, the correlation between IL-6 and hypertension risk is not statistically significant.

Journal Pre-proof