

https://dspace.org/

Circulating cytokines and risk of developing hypertension A System review andanalysis

E Caiazzo; M Sharma; A Rezig; M Morsy; Simone Crouch ...

ACADEMIC PRESS LTD- ELSEVIER SCIENCE LTD
https://hdl.handle.net/10539/41721
WOS

Downloaded from a DSpace repository. https://dspace.org/

Pharmacological Research 200 (2024) 107050



Contents lists available at ScienceDirect

Pharmacological Research

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



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

Elisabetta Caiazzo [a,b,1], Malvika Sharma [c,1], Asma O.M. Rezig [a,1], Moustafa I. Morsy [a], Marta Czesnikiewicz-Guzik [c,d], Armando Ialenti [b], Joanna Sulicka-Grodzicka [a,e], Pierpaolo Pellicori [f], Simone H. Crouch [g], Aletta E. Schutte [h,i,j,k], Dario Bruzzese [l], Pasquale Maffia [a,b,m,*,2], Tomasz J. Guzik [m,n,o,**,2]

[a] School of Infection & Immunity, College of Medical, Veterinary and Life Sciences, University of Glasgow, UK
[b] Department of Pharmacy, School of Medicine and Surgery, University of Naples Federico II, Naples, Italy
[c] School of Medicine, Dentistry and Nursing, College of Medical, Veterinary and Life Sciences, University of Glasgow, UK
[d] Department of Periodontology, Prophylaxis and Oral Medicine, Jagiellonian University, Krakow, Poland
[e] Department of Rheumatology and Immunology, Jagiellonian University Medical College, Kracow, Poland
[f] School of Cardiovascular and Metabolic Health, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK
[g] SA MRC/Wits Developmental Pathways for Health Research Unit (DPHRU), School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, South Africa
[h] Hypertension in Africa Research Team (HART), North-West University, Potchefstroom, South Africa
[i] MRC Research Unit: Hypertension and Cardiovascular Disease, North-West University, Potchefstroom, South Africa
[j] The George Institute for Global Health, Sydney, Australia
[k] School of Population Health, University of New South Wales, Sydney, Australia
[l] Department of Public Health, School of Medicine and Surgery, University of Naples Federico II, Naples, Italy
[m] Africa-Europe Cluster of Research Excellence in Non-Communicable Diseases & Multimorbidity, African Research Universities Alliance (ARUA) & The Guild of European Research-intensive Universities, South Africa
[n] Centre for Cardiovascular Science, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK
[o] Department of Internal and Agricultural Medicine and Omicron Medical Genomics Laboratory, Jagiellonian University Medical College, Krakow, Poland

ARTICLE INFO

Keywords:
Cytokines
Incident hypertension
Risk
Systematic review
Meta-analysis

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 $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg 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).

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.

* Correspondence to: School of Infection & Immunity, University of Glasgow, Glasgow, UK.
** Correspondence to: Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK.
E-mail addresses: Pasquale.Maffia@glasgow.ac.uk (P. Maffia), tguzik@exseed.ed.ac.uk (T.J. Guzik).
[1] These authors contributed equally to this work.
[2] These authors contributed equally to this work.

https://doi.org/10.1016/j.phrs.2023.107050
Received 10 September 2023; Received in revised form 27 December 2023; Accepted 27 December 2023
Available online 29 December 2023
1043-6618/© 2024 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Results: Only IL-6 and IL-1β levels have evidence allowing for quantitative evaluation concerning the onset of hypertension. Six studies (10406 participants, 2932 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.

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 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 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 $\geq$ 140 mmHg or diastolic blood pressure (DBP) $\geq$ 90 mmHg 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.

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 (Fig. 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).

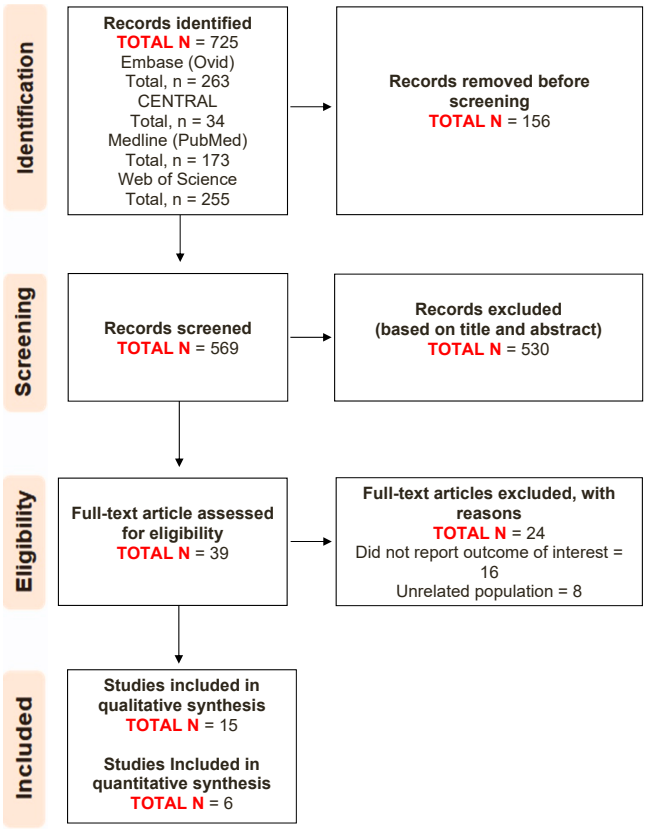


Fig. 1. Flow chart reporting the search strategy according to PRISMA.

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 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 Fig. 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.

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 2932 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 $\geq$ 140/90 mmHg) 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 (Fig. 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 (Fig. 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 (Fig. 2C; HR/RR: 1.24; 95% CI, 0.96 to 1.61; I^2 = 56%, n = 6). In sensitivity analysis, when we excluded

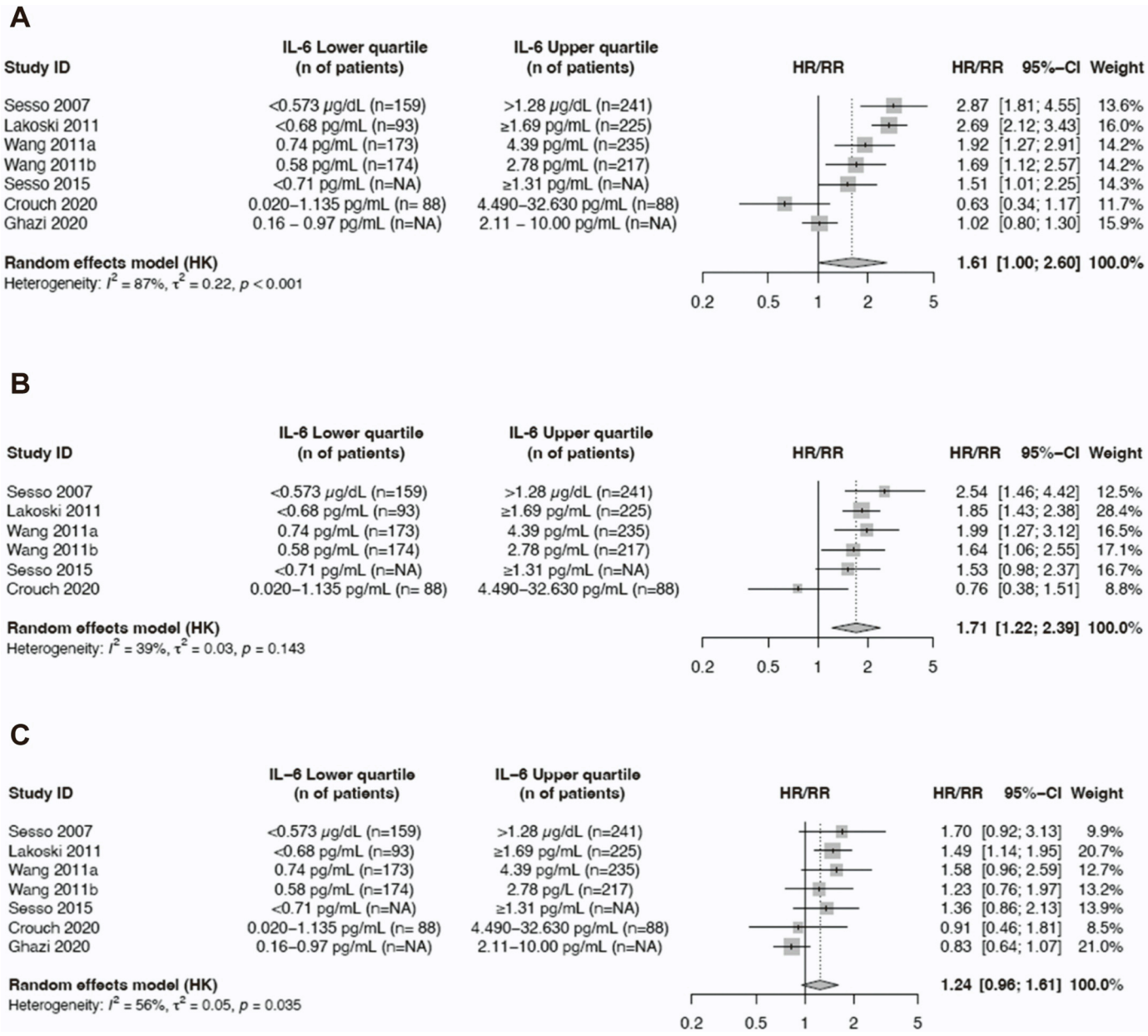


Fig. 2. Forest plots of pooled HR/RR of hypertension for the highest versus lowest quartile of IL-6. Hazard ratio (HR)/Risk ratio (RR) and 95% confidence interval (CI) from the eligible studies of the association between IL-6 circulating levels and incident hypertension estimates in a random effects 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.

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 (Fig. 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).

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 (Fig. 3), 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).

3.4. Other cytokines

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-

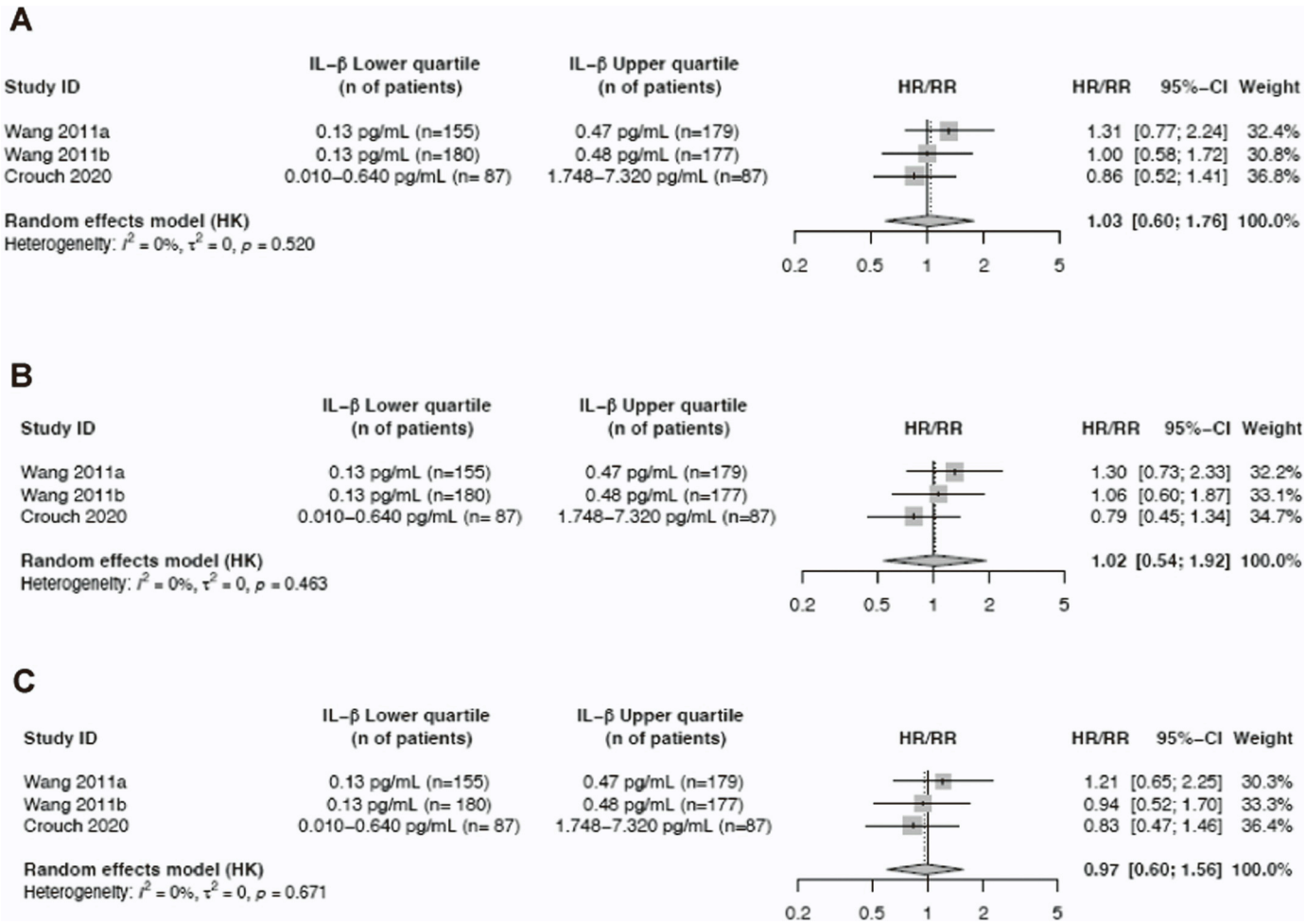


Fig. 3. Forest plots of pooled HR/RR of hypertension for the highest versus lowest quartile of IL-1β. Hazard ratio (HR)/Risk ratio (RR) and 95% confidence interval (CI) from the eligible studies of the association between IL-1β circulating levels and incident hypertension estimates in a random effects 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.

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).

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.

Funding

TJG is supported by the European Research Council (ERC and InflammaTENSION, ERC-CoG-726318); European Research Area - CVD (ERA-CVD) (BrainGutImmune (ERA-CVD/Gut-brain/8/2021 and ImmmuneHyperCog, NCBiR Poland), British Heart Foundation grants (FS/14/49/30838 and FS/4yPhD/F/20/34127A) and as part of the British Heart Foundation Centre for Research Excellence at the University of Edinburgh (RE/18/5/34216). PM is supported by British Heart Foundation grants (PG/19/84/34771, FS/19/56/34893A, PG/21/10541, PG/21/10557 and PG/21/10634), the Erasmus+ International Credit Mobility (ICM) (grant 2020–1-UK01-KA107–078782); and FRA 2020 - Linea A, University of Naples Federico II/Compagnia di San Paolo. AI is supported by the Italian Ministry of University and Research (MIUR) PRIN 2017 (2017NKB2N4_003) and PRIN 2020 (20203YAY9B).

CRediT authorship contribution statement

Rezig Asma Oumkaltoum: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Morsy Moustafa:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Czesnikiewicz-Guzik Marta:** Writing – review & editing. **Ialenti Armando:** Writing – review & editing. **Schutte Aletta E.:** Writing – review & editing. **Bruzzese Dario:** Formal analysis, Methodology, Software, Writing – review & editing. **Maffia Pasquale:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Guzik Tomasz Jan:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Caiazzo Elisabetta:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sharma Malvika:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Sulicka-Grodzicka Joanna:** Writing – review & editing. **Pellicori Pierpaolo:** Data curation, Supervision, Writing – review & editing. **Crouch Simone:** Data curation, Methodology, Writing – review & editing.

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.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2023.107050.

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] L. Liberale, F. Montecucco, L. Schwarz, T.F. Luscher, G.G. Camici, Inflammation and cardiovascular diseases: lessons from seminal clinical trials, Cardiovasc. Res. 117 (2021) 411–422.
[3] K.M. Cheema, E. Dicks, J. Pearson, N.J. Samani, Long-term trends in the epidemiology of cardiovascular diseases in the uk: insights from the british heart foundation statistical compendium, Cardiovasc. Res. 118 (2022) 2267–2280.
[4] R. Nosalski, E. McGinnigle, M. Siedlinski, T.J. Guzik, Novel immune mechanisms in hypertension and cardiovascular risk, Curr. Cardiovasc. Risk Rep. 11 (2017) 12.
[5] K.K. Griendling, L.L. Camargo, F.J. Rios, R. Alves-Lopes, A.C. Montezano, R. M. Touyz, Oxidative stress and hypertension, Circ. Res. 128 (2021) 993–1020.
[6] R.P. Brandes, Endothelial dysfunction and hypertension, Hypertension 64 (2014) 924–928.
[7] E.C. Murray, R. Nosalski, N. MacRitchie, M. Tomaszewski, P. Maffia, D.G. Harrison, et al., Therapeutic targeting of inflammation in hypertension: from novel mechanisms to translational perspective, Cardiovasc. Res. 117 (2021) 2589–2609.
[8] M. Siedlinski, E. Jozefczuk, X. Xu, A. Teumer, E. Evangelou, R.B. Schnabel, et al., White blood cells and blood pressure: a mendelian randomization study, Circulation 141 (2020) 1307–1317.
[9] T.P. Mikolajczyk, P. Szczepaniak, F. Vidler, P. Maffia, G.J. Graham, T.J. Guzik, Role of inflammatory chemokines in hypertension, Pharmacol. Ther. 223 (2021) 107799.
[10] C.U. Chae, R.T. Lee, N. Rifai, P.M. Ridker, Blood pressure and inflammation in apparently healthy men, Hypertension 38 (2001) 399–403.
[11] H. Nguyen, V.L. Chiasson, P. Chatterjee, S.E. Kopriva, K.J. Young, B.M. Mitchell, Interleukin-17 causes rho-kinase-mediated endothelial dysfunction and hypertension, Cardiovasc. Res. 97 (2013) 696–704.
[12] G.N. Dalekos, M. Elisaf, E. Bairaktari, O. Tsolas, K.C. Siamopoulos, 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. 129 (1997) 300–308.
[13] B. Chamarthi, G.H. Williams, V. Ricchiuti, N. Srikumar, P.N. Hopkins, J.M. Luther, et al., Inflammation and hypertension: the interplay of interleukin-6, dietary

sodium, and the renin-angiotensin system in humans, Am. J. Hypertens. 24 (2011) 1143–1148.
[14] A.A. Elmarakby, J.E. Quigley, J.D. Imig, J.S. Pollock, D.M. Pollock, Tnf-alpha inhibition reduces renal injury in doca-salt hypertensive rats, Am. J. Physiol. Regul. Integr. Comp. Physiol. 294 (2008) R76–R83.
[15] M.S. Madhur, H.E. Lob, L.A. McCann, Y. Iwakura, Y. Blinder, T.J. Guzik, et al., Interleukin 17 promotes angiotensin ii-induced hypertension and vascular dysfunction, Hypertension 55 (2010) 500–507.
[16] M.A. Saleh, W.G. McMaster, J. Wu, A.E. Norlander, S.A. Funt, S.R. Thabet, et al., Lymphocyte adaptor protein lnk deficiency exacerbates hypertension and end-organ inflammation, J. Clin. Investig. 125 (2015) 1189–1202.
[17] P. Crosswhite, Z. Sun, Ribonucleic acid interference knockdown of interleukin 6 attenuates cold-induced hypertension, Hypertension 55 (2010) 1484–1491.
[18] D.L. Lee, L.C. Sturgis, H. Labazi, J.B., Jr Osborne, C. Fleming, J.S. Pollock, et al., Angiotensin ii hypertension is attenuated in interleukin-6 knockout mice, Am. J. Physiol. Heart Circ. Physiol. 290 (2006) H935–H940.
[19] M. Gonzalez-Amor, A.B. Garcia-Redondo, I. Jorge, G. Zalba, M. Becares, M.J. Ruiz-Rodriguez, 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. 118 (2022) 3250–3268.
[20] A.M. Abdelrahman, Y.M. Al Suleimani, M. Ashique, P. Manoj, B.H. Ali, Effect of infliximab and tocilizumab on fructose-induced hyperinsulinemia and hypertension in rats, Biomed. Pharm. 105 (2018) 182–186.
[21] A.P. Faria, A.M.V. Ritter, A. Santa-Catharina, D.P. Souza, E.P. Naseri, M.B. Bertolo, 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. 116 (2021) 443–451.
[22] A.M. Rothman, J. MacFadyen, T. Thuren, A. Webb, D.G. Harrison, T.J. Guzik, et al., Effects of interleukin-1beta inhibition on blood pressure, incident hypertension, and residual inflammatory risk: a secondary analysis of cantos, Hypertension 75 (2020) 477–482.
[23] S.A. Provan, I.J. Berg, H.B. Hammer, A. Mathiessen, T.K. Kvien, A.G. Semb, 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 10 (2015) e0130709.
[24] R. Schindler, C.A. Dinarello, K.M. Koch, Angiotensin-converting-enzyme inhibitors suppress synthesis of tumour necrosis factor and interleukin 1 by human peripheral blood mononuclear cells, Cytokine 7 (1995) 526–533.
[25] A.C. Peeters, M.G. Netea, B.J. Kullberg, T. Thien, J.W. van der Meer, The effect of renin-angiotensin system inhibitors on pro- and anti-inflammatory cytokine production, Immunology 94 (1998) 376–379.
[26] G. Vazquez-Oliva, J.M. Fernandez-Real, A. Zamora, M. Vilaseca, L. Badimon, Lowering of blood pressure leads to decreased circulating interleukin-6 in hypertensive subjects, J. Hum. Hypertens. 19 (2005) 457–462.
[27] Z.H. Zhang, S.G. Wei, J. Francis, R.B. Felder, Cardiovascular and renal sympathetic activation by blood-borne tnf-alpha in rat: the role of central prostaglandins, Am. J. Physiol. Regul. Integr. Comp. Physiol. 284 (2003) R916–R927.
[28] Y. Funakoshi, T. Ichiki, K. Ito, A. Takeshita, Induction of interleukin-6 expression by angiotensin ii in rat vascular smooth muscle cells, Hypertension 34 (1999) 118–125.
[29] Y. Han, M.S. Runge, A.R. Brasier, Angiotensin ii induces interleukin-6 transcription in vascular smooth muscle cells through pleiotropic activation of nuclear factor-kappa b transcription factors, Circ. Res. 84 (1999) 695–703.
[30] M. Ruiz-Ortega, M. Ruperez, O. Lorenzo, V. Esteban, J. Blanco, S. Mezzano, et al., Angiotensin ii regulates the synthesis of proinflammatory cytokines and chemokines in the kidney, Kidney Int. Suppl. (2002) S12–S22.
[31] D. Sanz-Rosa, M.P. Oubina, E. Cediel, N. de Las Heras, O. Vegazo, J. Jimenez, 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. 288 (2005) H111–H115.
[32] S. Kany, J.T. Vollrath, B. Relja, Cytokines in inflammatory disease, Int. J. Mol. Sci. 20 (2019).
[33] S.M. Opal, V.A. DePalo, Anti-inflammatory cytokines, Chest 117 (2000) 1162–1172.
[34] E. Caiazzo, A.O.M. Rezig, D. Bruzzese, A. Ialenti, C. Cicala, J.G.F. Cleland, 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, Pharm. Res. 176 (2022) 106053.
[35] P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease, New Engl. J. Med. 377 (2017) 1119–1131.
[36] P.M. Ridker, From rescue to zeus: will interleukin-6 inhibition with ziltivekimab prove effective for cardiovascular event reduction? Cardiovasc. Res. 117 (2021) e138–e140.
[37] L.E. Bautista, L.M. Vera, I.A. Arenas, G. Gamarra, Independent association between inflammatory markers (c-reactive protein, interleukin-6, and tnf-alpha) and essential hypertension, J. Hum. Hypertens. 19 (2005) 149–154.
[38] L. Ghazi, J.V. Baker, S. Sharma, M.K. Jain, A. Palfreeman, C. Necsoi, et al., Role of inflammatory biomarkers in the prevalence and incidence of hypertension among hiv-positive participants in the start trial, Am. J. Hypertens. 33 (2020) 43–52.
[39] S.G. Lakoski, M. Cushman, D.S. Siscovick, R.S. Blumenthal, W. Palmas, G. Burke, et al., The relationship between inflammation, obesity and risk for hypertension in the multi-ethnic study of atherosclerosis (mesa), J. Hum. Hypertens. 25 (2011) 73–79.
[40] H.D. Sesso, L. Wang, J.E. Buring, P.M. Ridker, J.M. Gaziano, Comparison of interleukin-6 and c-reactive protein for the risk of developing hypertension in women, Hypertension 49 (2007) 304–310.
[41] H.D. Sesso, M.C. Jimenez, L. Wang, P.M. Ridker, J.E. Buring, J.M. Gaziano, Plasma inflammatory markers and the risk of developing hypertension in men, J. Am. Heart Assoc. 4 (2015) e001802.
[42] L. Wang, J.E. Manson, J.M. Gaziano, S. Liu, B. Cochrane, N.R. Cook, et al., Circulating inflammatory and endothelial markers and risk of hypertension in white and black postmenopausal women, Clin. Chem. 57 (2011) 729–736.
[43] S.H. Crouch, S. Botha-Le Roux, C. Delles, L.A. Graham, A.E. Schutte, Inflammation and hypertension development: a longitudinal analysis of the african-predict study, Int. J. Cardiol. Hypertens. 7 (2020) 100067.
[44] A.E. Schutte, P.N. Gona, C. Delles, A.S. Uys, A. Burger, C.M. Mels, 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. 26 (2019) 458–470.
[45] E. Nakao, H. Adachi, M. Enomoto, A. Fukami, E. Kumagai, S. Nakamura, 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. 30 (2017) 808–814.
[46] K. Sahakyan, B.E. Klein, C.E. Myers, M.Y. Tsai, R. Klein, Novel risk factors in long-term hypertension incidence in type 1 diabetes mellitus, Am. Heart J. 159 (2010) 1074–1080.
[47] J.H. Gordon, M.J. LaMonte, J. Zhao, R.J. Genco, T.R. Cimato, K.M. Hovey, et al., The association between serum inflammatory biomarkers and incident hypertension among postmenopausal women in the buffalo osteoperio study, J. Hum. Hypertens. 35 (2021) 791–799.
[48] B.M. Cheung, K.L. Ong, A.W. Tso, R.Y. Leung, S.S. Cherny, P.C. Sham, et al., Relationship of plasma interleukin-6 and its genetic variants with hypertension in hong kong chinese, Am. J. Hypertens. 24 (2011) 1331–1337.
[49] M. Pavuk, T.C. Serio, C. Cusack, M. Cave, P.F. Rosenbaum, L.S. Birnbaum, Hypertension in relation to dioxins and polychlorinated biphenyls from the anniston community health survey follow-up, Environ. Health Perspect. 127 (2019) 127007.
[50] H.J. Yoo, M. Kim, S.H. Lee, J.H. Lee, 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] V. Mauno, K. Hannu, K. Esko, Proinflammation and hypertension: a population-based study, Mediat. Inflamm. 2008 (2008) 619704.
[52] B.E. Barton, The biological effects of interleukin 6, Med. Res. Rev. 16 (1996) 87–109.
[53] L.I. Schrader, D.A. Kinzenbaw, A.W. Johnson, F.M. Faraci, S.P. Didion, Il-6 deficiency protects against angiotensin ii induced endothelial dysfunction and hypertrophy, Arterioscler. Thromb. Vasc. Biol. 27 (2007) 2576–2581.
[54] J.R. Gomolak, S.P. Didion, Angiotensin ii-induced endothelial dysfunction is temporally linked with increases in interleukin-6 and vascular macrophage accumulation, Front. Physiol. 5 (2014) 396.
[55] A. Jayedi, K. Rahimi, L.E. Bautista, M. Nazarzadeh, M.S. Zargar, S. Shab-Bidar, Inflammation markers and risk of developing hypertension: a meta-analysis of cohort studies, Heart 105 (2019) 686–692.
[56] M. Kuwabara, R. Kuwabara, K. Niwa, I. Hisatome, G. Smits, C.A. Roncal-Jimenez, et al., Different risk for hypertension, diabetes, dyslipidemia, and hyperuricemia according to level of body mass index in japanese and american subjects, Nutrients 10 (2018).
[57] J.E. Neter, B.E. Stam, F.J. Kok, D.E. Grobbee, J.M. Geleijnse, Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials, Hypertension 42 (2003) 878–884.
[58] X. Xu, J.M. Eales, X. Jiang, E. Sanderson, M. Drzal, S. Saluja, et al., Contributions of obesity to kidney health and disease: insights from mendelian randomization and the human kidney transcriptomics, Cardiovasc Res. 118 (2022) 3151–3161.
[59] R.H. Straub, H.W. Hense, T. Andus, J. Scholmerich, G.A. Riegger, H. Schunkert, Hormone replacement therapy and interrelation between serum interleukin-6 and body mass index in postmenopausal women: a population-based study, J. Clin. Endocrinol. Metab. 85 (2000) 1340–1344.
[60] R.H. Werida, N.M. El-Gharbawy, T.M. Mostafa, Circulating il-6, clusterin and irisin in obese subjects with different grades of obesity: association with insulin resistance and sexual dimorphism, Arch. Endocrinol. Metab. 65 (2021) 126–136.
[61] V. Mohamed-Ali, S. Goodrick, A. Rawesh, D.R. Katz, J.M. Miles, J.S. Yudkin, et al., Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo, J. Clin. Endocrinol. Metab. 82 (1997) 4196–4200.
[62] F.M. Schmidt, J. Weschenfelder, C. Sander, J. Minkwitz, J. Thormann, T. Chittka, et al., Inflammatory cytokines in general and central obesity and modulating effects of physical activity, PLoS One 10 (2015) e0121971.
[63] L.L. Camargo, A.C. Montezano, M. Hussain, Y. Wang, Z. Zou, F.J. Rios, et al., Central role of c-src in nox5- mediated redox signalling in vascular smooth muscle cells in human hypertension, Cardiovasc Res. 118 (2022) 1359–1373.
[64] M. Sagris, A.S. Antonopoulos, P. Theofilis, E. Oikonomou, G. Siasos, S. Tsalamandris, et al., Risk factors profile of young and older patients with myocardial infarction, Cardiovasc Res. 118 (2022) 2281–2292.
[65] J.S. Yudkin, M. Kumari, S.E. Humphries, V. Mohamed-Ali, Inflammation, obesity, stress and coronary heart disease: is interleukin-6 the link? Atherosclerosis 148 (2000) 209–214.
[66] C. Gazzaruso, R. Bruno, A. Garzaniti, S. Giordanetti, P. Fratino, P. Sacchi, et al., Hypertension among hiv patients: prevalence and relationships to insulin resistance and metabolic syndrome, J. Hypertens. 21 (2003) 1377–1382.

[67] R.N. Peck, R. Shedafa, S. Kalluvya, J.A. Downs, J. Todd, M. Suthanthiran, et al., Hypertension, kidney disease, hiv and antiretroviral therapy among tanzanian adults: a cross-sectional study, BMC Med. 12 (2014) 125.
[68] Y. Xu, X. Chen, K. Wang, Global prevalence of hypertension among people living with hiv: a systematic review and meta-analysis, J. Am. Soc. Hypertens. 11 (2017) 530–540.
[69] C.U. Nduka, S. Stranges, A.M. Sarki, P.K. Kimani, O.A. Uthman, 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. 30 (2016) 355–362.
[70] N.F. Onen, E.T. Overton, W. Seyfried, E.R. Stumm, M. Snell, K. Mondy, et al., Aging and hiv infection: a comparison between older hiv-infected persons and the general population, HIV Clin. Trials 11 (2010) 100–109.
[71] S.A. Fahme, G.S. Bloomfield, R. Peck, Hypertension in hiv-infected adults: Novel pathophysiologic mechanisms, Hypertension 72 (2018) 44–55.
[72] A.S. Batavia, P. Severe, M.H. Lee, A. Apollon, Y.S. Zhu, K.M. Dupnik, et al., Blood pressure and mortality in a prospective cohort of hiv-infected adults in port-au-prince, haiti, J. Hypertens. 36 (2018) 1533–1539.
[73] S. Okello, S.B. Asiimwe, M. Kanyesigye, W.R. Muyindike, Y., 2nd Boum, B. B. Mwebesa, 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. 73 (2016) 396–402.
[74] S. Botha, C.M.T. Fourie, R. Schutte, J. Eugen-Olsen, R. Pretorius, A.E. Schutte, Soluble urokinase plasminogen activator receptor as a prognostic marker of all-cause and cardiovascular mortality in a black population, Int. J. Cardiol. 184 (2015) 631–636.
[75] J. Bullenkamp, V. Mengoni, S. Kaur, I. Chhetri, P. Dimou, Z.M.J. Astroulakis, et al., Interleukin-7 and interleukin-15 drive cd4+cd28null t lymphocyte expansion and function in patients with acute coronary syndrome, Cardiovasc. Res. 117 (2021) 1935–1948.
[76] Y. Alexander, E. Osto, A. Schmidt-Trucksass, M. Shechter, D. Trifunovic, D. J. Duncker, 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. 117 (2021) 29–42.
[77] P. Welsh, G. Grassia, S. Botha, N. Sattar, P. Maffia, Targeting inflammation to reduce cardiovascular disease risk: a realistic clinical prospect? Br. J. Pharmacol. 174 (2017) 3898–3913.
[78] N.R. Pugliese, P. Pellicori, F. Filidei, N. De Biase, P. Maffia, T.J. Guzik, et al., Inflammatory pathways in heart failure with preserved left ventricular ejection fraction: implications for future interventions, Cardiovasc. Res. 118 (2023) 3536–3555.
[79] P.C. Evans, S.M. Davidson, J. Wojta, M. Back, S. Bollini, M. Brittan, et al., From novel discovery tools and biomarkers to precision medicine-basic cardiovascular science highlights of 2021/22, Cardiovasc. Res. 118 (2022) 2754–2767.
[80] J. Hettwer, J. Hinterdobler, B. Miritsch, M.A. Deutsch, X. Li, C. Mauersberger, et al., Interleukin-1beta suppression dampens inflammatory leucocyte production and uptake in atherosclerosis, Cardiovasc. Res. 118 (2022) 2778–2791.