ORIGINAL RESEARCH ARTICLE

# Inflammation markers and risk of developing hypertension: a meta-analysis of cohort studies

Ahmad Jayedi,[1] Kazem Rahimi,[2,3] Leonelo E Bautista,[4] Milad Nazarzadeh,[2,5] Mahdieh Sadat Zargar,[6] Sakineh Shab-Bidar[7]

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[1]Food (salt) Safety Research Center, Semnan University of Medical Sciences, Semnan, Iran
[2]George Institute for Global Health, University of Oxford, Oxford, UK
[3]Deep Medicine, Oxford Martin School, University of Oxford, Oxford, UK
[4]Department of Population Health, School of Medicine, University of Wisconsin at Madison, Wisconsin, USA
[5]Collaboration Center of Meta-Analysis Research, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran
[6]Nursing Care Research Center, Semnan University of Medical Sciences, Semnan, Iran
[7]Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

**Correspondence to**
Dr Sakineh Shab-Bidar, Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran 14155/6117, Iran; s_shabbidar@tums.ac.ir

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## ABSTRACT

**Objective** To systematically assess the association of circulating inflammation markers with the future risk of hypertension.

**Methods** We did a systematic literature search of PubMed and Scopus, from database inception to July 10, 2018. Prospective and retrospective cohort studies evaluating the association of circulating C reactive protein (CRP), high-sensitive CRP (hs-CRP), interleukin 6 (IL-6) and IL-1β to the risk of developing hypertension in the general population were included. The relative risks (RRs) for the top versus bottom tertiles of circulating biomarkers were calculated using a fixed-effects/random-effects model. A potential non-linear dose-response association was tested.

**Results** Fourteen prospective cohort studies, two retrospective cohort studies and five nested case-control studies involving 142 640 participants and 20 676 cases were identified. The RR for the third versus first tertiles of circulating CRP was 1.23 (95% CI 1.11 to 1.35; $I^2$=59%, n=12). The association remained unchanged after adjustment for body mass index. The RRs for other biomarkers were as follows: hs-CRP (RR 1.20, 95% CI 1.02 to 1.37; $I^2$=74%, n=7), IL-6 (RR 1.51, 95% CI 1.30 to 1.71; $I^2$=0%, n=5), and IL-1β (RR 1.22, 95% CI 0.92 to 1.51; $I^2$=0%, n=3). A non-linear dose-response meta-analysis demonstrated that the risk of hypertension increased linearly with increasing circulating inflammation markers, even within the low-risk and intermediate-risk categories.

**Conclusions** Higher levels of circulating CRP, hs-CRP and IL-6, but not IL-1β, were associated with the risk of developing hypertension. The association persisted in subgroups of studies defined by major sources of heterogeneity.

## INTRODUCTION

High blood pressure is a major risk factor for cardiovascular morbidity, mortality and disability worldwide. About a quarter of the world's population has hypertension (systolic blood pressure (SBP)≥140 and diastolic blood pressure (DBP)≥90 mm Hg).[1] Although hypertension is easy to diagnose and effective treatments are available, only a third of those receiving pharmacological treatment for hypertension have their blood pressure controlled.[2] In consequence, there is a pressing need to identify novel risk factors for hypertension, potentially useful for risk stratification and for development of preventive interventions.

Recent studies suggest that systemic inflammation may play a role in the pathogenesis and progression of hypertension.[3] A few cross-sectional studies have shown a positive association between levels of circulating inflammation markers and elevated blood pressure.[4 5] However, findings from cross-sectional studies could be explained by reverse causality bias, since hypertension may be a driver of inflammation.[6] On the other hand, a significant association has been reported in some[7–9] but not all cohort studies,[10–13] while uncertainties in the estimate of the association have compromised the conclusions of other cohort studies.[14–18]

In spite of current uncertainty, no previous study has summarised the existing evidence of the role of elevated inflammation markers on the risk of hypertension. We therefore conducted a meta-analysis of prospective and retrospective cohort studies to evaluate if high levels of circulating inflammation markers (C reactive protein (CRP), high-sensitive CRP (hs-CRP), IL-6 and IL-1β) are associated with an increased risk of hypertension in the general population.

## METHODS

### Search strategy

To find potentially relevant studies, we searched articles in English referenced in PubMed and Scopus, from database inception to 10 July 2018, using a combination of keywords relevant to inflammation, hypertension and study design (online supplementary file 1). The reference lists of retrieved articles were reviewed for additional eligible studies.

### Eligibility and study selection

Two authors (AJ, MSZ) independently reviewed the titles and abstracts of all articles retrieved, and selected those meeting the following criteria: (1) Based on prospective and retrospective cohort, nested case-control or case-cohort studies. (2) Conducted in adults aged 18 years or older. (3) Reporting circulating levels of inflammation markers (CRP, hs-CRP, IL-6 and IL-1β) as exposure. (4) Reporting the incidence of hypertension. (5) Reporting the effect of the exposure in the form of a relative risk (RR: risk ratio, OR or HR) and its 95% CI. Cross-sectional and case-control studies, as well as studies in patient populations were excluded.

### Data extraction and quality assessment

Two investigators (AJ, MSZ) independently extracted the following information from eligible

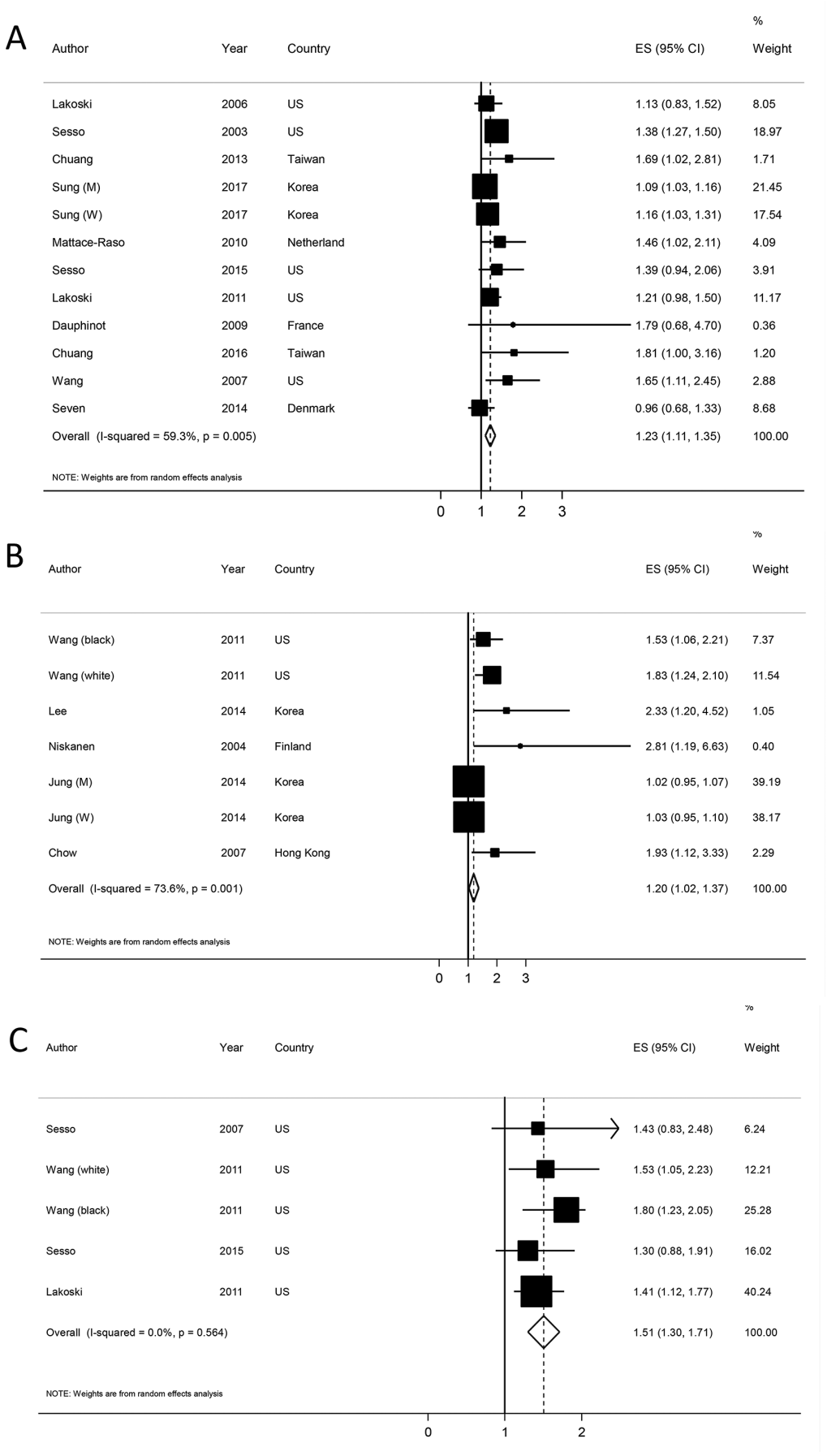


**Figure 1** Relative risk of hypertension for the top versus bottom tertiles of circulating inflammation markers (A) C reactive protein. (B) High-sensitive C reactive protein. (C) IL-6. ES: effect size.

**Table 1** Relative risk of hypertension for the third compared with the first tertiles of circulating C reactive protein

| | | n | Participants | RR (95% CI) | $I^2$(%), $P_{heterogeneity}$* | $P_{between}$† |
|---|---|---|---|---|---|---|
| All studies | | 12 | 137 916 | 1.23 (1.11 to 1.35) | 59%, 0.005 | – |
| Sex | | | | | | |
| Men | | 3 | 57 746 | 1.10 (1.03 to 1.16) | 0%, 0.54 | 0.003 |
| Women | | 3 | 64 096 | 1.25 (1.06 to 1.44) | 69%, 0.04 | |
| Both | | 8 | 19 993 | 1.22 (1.05 to 1.39) | 7%, 0.37 | |
| Age (mean) | | | | | | |
| <50 years | | 7 | 110 420 | 1.11 (1.05 to 1.16) | 0%, 0.44 | <0.001 |
| ≥50 years | | 5 | 27 496 | 1.36 (1.26 to 1.47) | 0%, 0.66 | |
| Geographical region | | | | | | |
| USA | | 5 | 30 235 | 1.34 (1.24 to 1.44) | 0%, 0.45 | <0.001 |
| Europe | | 3 | 4853 | 1.17 (0.77 to 1.57) | 30%, 0.24 | |
| Asia | | 4 | 102 828 | 1.13 (1.02 to 1.23) | 26%, 0.25 | |
| Definition of hypertension | | | | | | |
| SBP≥140, DBP≥90 mm Hg and/or antihypertension treatment | | 10 | 135 944 | 1.22 (1.09 to 1.34) | 65%, 0.002 | 0.47 |
| SBP≥135, DBP≥85 mm Hg and/or antihypertension treatment | | 1 | 1637 | 1.79 (0.68 to 4.70) | – | |
| Isolated systolic hypertension | | 1 | 335 | 1.46 (1.02 to 2.11) | – | |
| Number of cases | | | | | | |
| <500 | | 7 | 13 133 | 1.24 (1.03 to 1.45) | 11%, 0.34 | 0.62 |
| >500 | | 5 | 124 783 | 1.22 (1.06 to 1.37) | 80%,<0.001 | |
| Adjustment for confounders | | | | | | |
| Alcohol consumption | Yes | 8 | 130 288 | 1.21 (1.07 to 1.35) | 71%, 0.001 | 0.27 |
| | No | 4 | 7628 | 1.29 (1.07 to 1.52) | 0%, 0.63 | |
| Physical activity | Yes | 8 | 130 288 | 1.21 (1.07 to 1.35) | 71%, 0.001 | 0.27 |
| | No | 4 | 7628 | 1.29 (1.07 to 1.52) | 0%, 0.63 | |
| Smoking | Yes | 9 | 130 288 | 1.21 (1.09 to 1.33) | 67%, 0.002 | 0.08 |
| | No | 3 | 7628 | 1.74 (1.09 to 2.40) | 0%, 0.98 | |
| Body mass index | Yes | 7 | 123 814 | 1.23 (1.08 to 1.37) | 71%, 0.002 | 0.72 |
| | No | 5 | 14 102 | 1.26 (0.98 to 1.54) | 36%, 0.18 | |
| Baseline blood pressure | Yes | 7 | 107,15 | 1.11 (1.05 to 1.17) | 0%, 0.44 | <0.001 |
| | No | 5 | 30 801 | 1.37 (1.26 to 1.47) | 0%, 0.53 | |

*$P_{heterogeneity}$ within subgroups with the use of a random-effects model.
†$P_{heterogeneity}$ between subgroups with the use of a fixed-effects model.
DBP, diastolic blood pressure; RR, relative risk; SBP, systolic blood pressure.

studies: first author's name, publication year, study name, country, age range and/or mean age (years), number of participants, hypertension diagnostic criteria, exposure levels, RR and its 95% CI for each exposure category, and confounding factors included in the multivariate analysis. We selected the RR from the model with the most comprehensive covariate adjustment. We used the Newcastle-Ottawa Scale to assess the quality of the studies included.[19] Any discrepancies were resolved through discussion under supervision a senior author (SS-B).

## Statistical analysis

We conducted separate meta-analyses for CRP, hs-CRP, IL-6 and IL-1β. We calculated the average RRs for the third compared with the first tertiles of the inflammation markers using a fixed-effects model. For studies that did not define exposed and non-exposed cohorts using tertiles of the marker, for the purpose of data analysis, we translated the effect of the marker on the incidence of hypertension to a risk ratio corresponding to a comparison between individuals in the upper and lower tertiles of the marker (online supplementary file 2).[20] A random-effects model was used[21] if there was evidence of significant heterogeneity ($I^2$ >50%, $p_{heterogeneity}$ <0.05).[22]

We evaluated the influence of each study on the average RR, by re-estimating the RR after excluding each study at a time. We also conducted subgroup analyses by gender, geographical location, number of hypertension cases and adjustment for main confounders (baseline blood pressure, physical activity, smoking, body mass index (BMI) and alcohol intake). The $I^2$ statistic and Cochran's Q test of heterogeneity were used to evaluate between-study heterogeneity.[22] Publication bias was assessed using funnel plots' asymmetry and tested with Egger's asymmetry test[23] and Begg's test (p<0.10),[24] when there were at least 10 studies.

We also tested for a non-linear dose-response when at least three studies were available. For this purpose, we modelled the

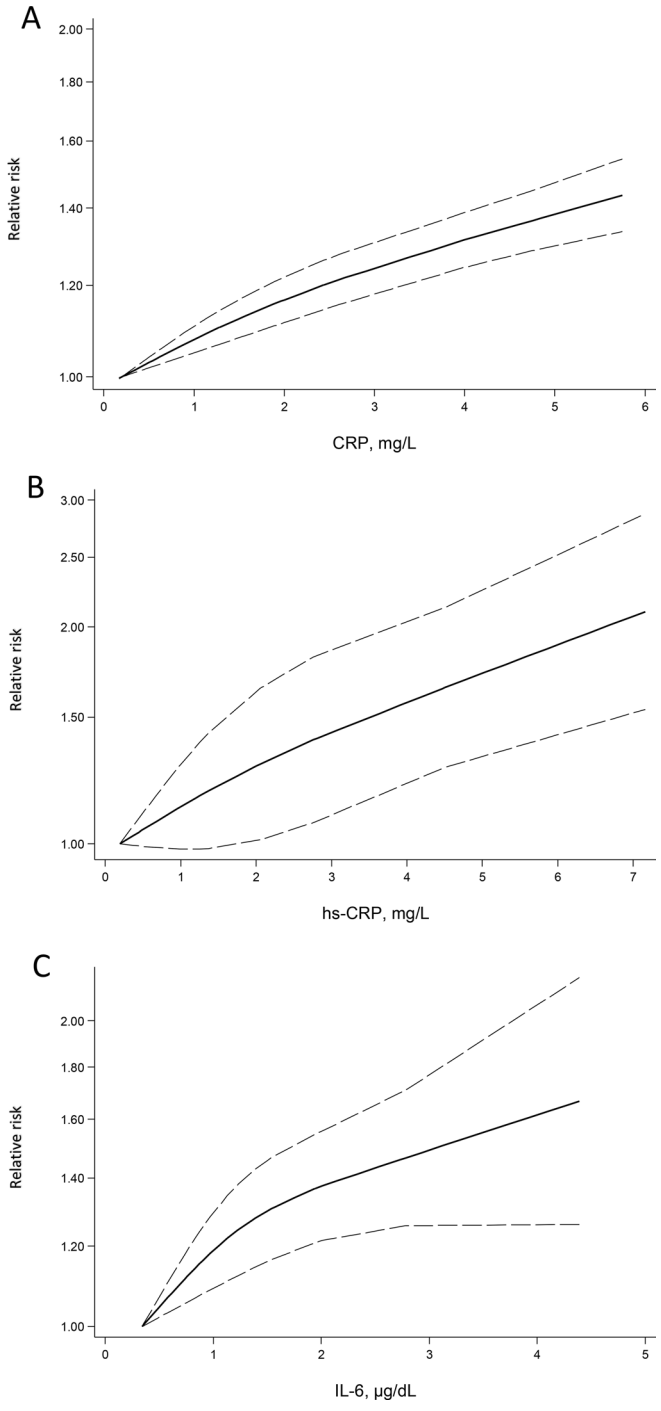


**Figure 2** Dose-response associations between circulating inflammation markers and risk of developing hypertension. CRP, C reactive protein; hs-CRP, high-sensitive C reactive protein.

inflammation marker using restricted cubic splines with three knots at fixed percentiles (10%, 50% and 90%) of the distribution,[25] fitted a regression model with the RR as dependent variable and tested whether the coefficient for the second spline was statistically different from zero. For the purpose of this analysis, if the numbers of participants/cases or person-years were not reported in the primary studies, we estimated them by dividing the total numbers by the number of exposure groups, if the exposure was defined as quantiles. All analyses were conducted with Stata software, V.13 (StataCorp, College Station, Texas, USA).

## RESULTS

The initial systematic search identified 10 235 potentially eligible publications. Of these, 10 103 publications were not relevant based on the review of the abstract (online supplementary file 3). Eventually, 132 articles were fully reviewed for inclusion in the meta-analysis. Only 18 articles were eligible for the meta-analysis. Reasons for excluding studies are described in online supplementary file 3. Three articles reported separate results for men and women,[9 11] and blacks and whites,[26] and estimates were separately included in the present meta-analysis. Thus, a total of 21 studies (18 articles) with 142 640 participants and 20 676 incident cases of hypertension were included in the meta-analysis.[7–18 26–31] We included in our analysis one study with isolated systolic hypertension in participants with a mean age of 64 years as the outcome,[27] because isolated systolic hypertension is the most frequent type of hypertension in patients ≥60 years old.

Two studies (one article) were retrospective cohort studies,[9] five (four articles) were nested case-control studies[13 14 26 28] and the rest were prospective cohort studies. Eight studies (six articles) were from Asia,[9 11 14–17] eight (seven articles) from USA[7 8 12 13 26 28 31] and five from Europe.[10 18 27 29 30] Of the 21 studies, 16 controlled for smoking, 14 controlled for physical activity and BMI, 13 controlled for alcohol intake, 11 for baseline blood pressure and 2 for dietary sodium intake. All studies excluded participants with a history of hypertension at baseline. All but two studies on CRP defined hypertension as SBP/DBP ≥140/90 mm Hg or taking antihypertension medication, the standard approach in epidemiological studies. One study on CRP[27] focused on isolated hypertension, defined as (SBP ≥160 mm Hg and DBP <90 mm Hg), and another[10] defined hypertension as SBP/DBP ≥135/85 mm Hg or using antihypertension medication. All studies on Hs-CRP and IL-6 used the standard definition of hypertension. The general characteristics of the studies are presented in online supplementary file 4, and the numbers of participants/cases and reported RRs across categories of inflammation markers are presented in online supplementary file 5.

### C reactive protein

Twelve studies (11 articles) were included in the analysis of CRP and risk of hypertension.[7–10 12 15 16 27–29 31] The RR of hypertension for the top versus bottom tertiles of CRP was 1.17 (95% CI 1.12 to 1.22) for the fixed-effects model and 1.23 (95% CI 1.11 to 1.35) for the random-effects model. There was moderate-to-high evidence of heterogeneity, $I^2$=59.3%, $p_{heterogeneity}$=0.005; (figure 1A). The influence analysis showed two large studies were the main sources of heterogeneity.[8 9] Excluding the Women's Health Study[8] changed the RR to 1.14 (95% CI 1.06 to 1.21; $I^2$=8%) and excluding Sung *et al*'s study[9] changed the RR to 1.30 (95% CI 1.17 to 1.42; $I^2$=14%).

Findings were consistent, regardless of the definition of hypertension used in the study ($p_{heterogeneity}$=0.47). However, gender, study region and adjustment for smoking were major sources of heterogeneity in the effect of CRP on the risk of hypertension (table 1). Indeed, the association was significantly stronger in women (RR 1.25) than in men (RR 1.10); in studies conducted in USA (RR 1.34) than in those conducted in Europe (RR 1.17) and Asia (RR: 1.13); in studies with participants with a mean age ≥50 years (RR 1.36) than in those with a mean age <50 years (RR 1.11); and in studies that did not adjust for smoking (RR 1.74) than in those that adjusted (RR 1.21). A significant positive association persisted even after adjustment for BMI (RR

**Table 2** Relative risk of hypertension for the third compared with the first tertiles of circulating high-sensitive C reactive protein

| | | n | Participants | RR (95% CI) | $I^2$(%), $P_{heterogeneity}$* | $P_{between}$† |
|---|---|---|---|---|---|---|
| All studies | | 7 | 4194 | 1.20 (1.02 to 1.37) | 73.6%, 0.001 | – |
| Sex | | | | | | |
| Men | | 2 | 1155 | 1.38 (0.03 to 2.78) | 39.9%, 0.20 | 0.07 |
| Women | | 3 | 2377 | 1.43 (0.86 to 2.00) | 87.1%,<0.001 | |
| Both | | 2 | 662 | 2.05 (1.13 to 2.97) | 0%, 0.70 | |
| Age (mean) | | | | | | |
| <50 years | | 1 | 210 | 1.93 (1.12 to 3.33) | - | 0.11 |
| ≥50 years | | 6 | 3984 | 1.17 (1.00 to 1.37) | 75%, 0.001 | |
| Geographical region | | | | | | |
| USA | | 2 | 1600 | 1.72 (1.38 to 2.07) | 0%, 0.41 | <0.001 |
| Europe | | 1 | 379 | 2.81 (1.19 to 6.63) | - | |
| Asia | | 4 | 2215 | 1.03 (0.95 to 1.12) | 39.9%, 0.17 | |
| Adjustment for confounders | | | | | | |
| Alcohol consumption | Yes | 4 | 2431 | 1.76 (1.43 to 2.20) | 0%, 0.63 | <0.001 |
| | No | 3 | 1763 | 1.03 (0.97 to 1.09) | 23.7%, 0.27 | |
| Physical activity | Yes | 6 | 3984 | 1.17 (1.00 to 1.34) | 75.2%, 0.001 | 0.11 |
| | No | 1 | 210 | 1.93 (1.12 to 3.33) | - | |
| Smoking | Yes | 6 | 3984 | 1.17 (1.00 to 1.34) | 75.2%, 0.001 | 0.11 |
| | No | 1 | 210 | 1.93 (1.12 to 3.33) | – | |
| Body mass index | Yes | 4 | 2215 | 1.03 (0.95 to 1.12) | 39.9%, 0.17 | <0.001 |
| | No | 3 | 1979 | 1.74 (1.40 to 2.08) | 0%, 0.53 | |
| Baseline blood pressure | Yes | 5 | 2594 | 1.04 (0.95 to 1.13) | 39.8%, 0.16 | <0.001 |
| | No | 2 | 1600 | 1.72 (1.38 to 2.07) | 0%, 0.41 | |

*$P_{heterogeneity}$ within subgroups with the use of a random-effects model.
†$P_{heterogeneity}$ between subgroups with the use of a fixed-effects model.
RR, relative risk.

1.23, 95% CI 1.08 to 1.37; $I^2$=71%, n=7 studies). On the other hand, there was no evidence of significant publication or small-studies bias (Egger's test p=0.15; Begg's test p=0.12; online supplementary file 6).

Seven studies (six articles) included sufficient data for the dose-response meta-analysis.[7–9 12 16 28] The risk of hypertension increased linearly with increasing circulating CRP concentration (*p* for non-linearity=0.07, figure 2A).

### High-sensitive CRP

Seven studies (five articles) were included in the analysis of hs-CRP.[11 14 17 18 26] The RR for the top versus bottom tertiles of hs-CRP was 1.06 (95% CI 1.01 to 1.07) for the fixed-effects model and 1.20 (95% CI 1.02 to 1.37) for the random-effects model (figure 1B). There was significant between-study heterogeneity ($I^2$=73.6%, $p_{heterogeneity}$=0.001). The RR changed from 1.04 (95% CI 0.95 to 1.13) excluding the Women's Health Initiative Observational Study[26] to 1.78 (95% CI 1.46 to 2.10) excluding the Korean Genome and Epidemiology Study on Atherosclerosis Risk;[11] the two studies with the largest impact on heterogeneity.

A significant RR was observed in two studies conducted in USA (RR 1.72, 95% CI 1.38 to 2.07), but not in four studies in Asian populations (RR 1.03, 95% CI 0.95 to 1.12; table 2). Also, the association was not significant in studies that controlled for BMI (RR 1.03, 95% CI 0.95 to 1.12; n=4). On the other hand, the association was stronger in studies with participants with a mean age <50 years (RR 1.93) than in those with a mean age ≥50 years (RR 1.17), but not significantly so ($p_{heterogeneity}$=0.11).

Publication bias was not assessed due to the small number of studies (n<10). Finally, there was a positive linear association between circulating hs-CRP concentration and hypertension risk in three studies (two articles)[17 26] (p for non-linearity=0.61, figure 2B).

### Interleukin 6

Five studies (four articles) were included in the analysis for IL-6.[7 13 28 30] All of them were from USA, and controlled for smoking and alcohol consumption. Participants in the third tertile of IL-6 had a 51% higher risk of hypertension as compared with those in the first tertile (RR 1.51, 95% CI 1.30 to 1.71), with no evidence of significant heterogeneity, $I^2$=0%, $p_{heterogeneity}$=0.56 (figure 1C). The RR changed little when individual studies were excluded (between 1.41 and 1.57). There was a significant association among studies that controlled for physical activity (RR 1.57, 95% CI 1.31 to 1.84), but not in studies that controlled for BMI (RR 1.34, 95% CI 0.90 to 1.77; n=2). There was a monotonic association between circulating IL-6 concentration and hypertension risk, with a somewhat slower trend of increment in the risk within the higher circulating IL-6 concentrations (p for non-linearity=0.07, figure 2C).

### Interleukin 1β

A non-significant association between circulating IL-1β concentration and the risk of developing hypertension (RR 1.22, 95% CI 0.92 to 1.51; $I^2$=0%) was found in the three available studies (two articles).[26 30]

## DISCUSSION

In this meta-analysis we gathered all cohort studies of the association between inflammation markers and incident hypertension, and found that higher levels of CRP, hs-CRP and IL-6 increased

the risk of hypertension by 23%, 20% and 51%, respectively. We also found a linear association between levels of these markers and risk of hypertension. In contrast, IL-1β was not significantly associated to incident hypertension. Although the risk of hypertension increased linearly with the level of inflammatory markers, the cut point to identify exposed individuals varied across studies and was undefined in some studies.

Higher levels of CRP could increase the risk of hypertension by decreasing expression and activation of the nitric oxide synthase,[32] increasing the synthesis of endothelin-1[33] and impairing endothelium-dependent vasorelaxation.[34] IL-6 may increase the risk of hypertension by increasing hepatocyte synthesis of CRP.[35] IL-6 also impairs insulin signalling and activity, contributing to the development of insulin resistance,[36] one of the major mechanisms underlying the development of hypertension. Also, IL-6 plays a key role in the pathogenesis of angiotensin II-mediated hypertension.[37]

Although CRP and IL-6 may partly mediate the effect of obesity on the risk of hypertension,[38] the strength of the CRP-hypertension association changed little when the analysis was restricted to studies that controlled for BMI. For hs-CRP and IL-6, increases in the risk of hypertension were also observed in studies that adjusted for BMI. However, these increases were no longer statistically significant, which was likely due the smaller number of studies included in that analysis (four for hs-CRP and two for IL-6).

In an analysis by region, CRP and hs-CRP exhibited stronger associations with hypertension risk in USA than in Asia (RRs 1.34 vs 1.13 and 1.73 vs 1.03, respectively). This may be due to differences in the set of factors included as confounders in US and Asian studies. Indeed, none of the US studies in the analysis of hs-CRP controlled for measures of adiposity, and this may have resulted in an overestimate of the effect of this marker. Nevertheless, the issue of regional differences in the effect of inflammation markers should be explored in future studies.

The present meta-analysis had several strengths. We tested the association across different inflammation markers instead of an individual marker, and thereby, presented a relatively comprehensive perspective of the possible association of inflammation markers with the risk of developing hypertension. The study further shows that the association between circulating CRP and risk of hypertension was independent of BMI, and thereby, could add evidence to the existing evidence about the potential role of inflammatory pathways in the pathogenesis of hypertension. Finally, we showed the shape of the dose-response relations, especially in the analysis of CRP, which indicated that increasing the circulating concentration of CRP, even within the low-risk range, was associated with a significant higher risk of developing hypertension.

Our study had also some important limitations. First, we performed a meta-analysis of observational studies which are subject to residual confounding. As found in some of the original studies, higher levels of systemic inflammation are accompanied by unhealthy lifestyle-related behaviours such as smoking, alcohol consumption, low physical activity and higher adherence to western-style dietary patterns; as well as conditions such as general and abdominal adiposity, diabetes, dyslipidaemia and higher blood pressure levels;[12 13 16 17 28] these in turn are associated with a higher risk. Indeed, higher levels of circulating inflammation markers may reflect an unfavourable health status or an unhealthy style-related behaviour. So, it is difficult to statistically control for the confounding effects of these variables. Second, in the analyses of hs-CRP and IL-6, the association became non-significant when the analysis was restricted to studies that controlled for BMI. However, this was likely due to the smaller number of studies included in that analysis because only four studies in the analysis of hs-CRP and two studies in the analysis of IL-6 controlled for BMI. In addition, in the analysis of CRP, the association did not change in the subgroup of studies that controlled for BMI. Therefore, there remains uncertainty regarding to what degree obesity explains the effect of inflammatory markers on the incidence of hypertension. Third, the number of studies was low in the analyses of hs-CRP, IL-6 and IL-1β; and all of the studies in the analysis of IL-6 were from USA. In addition, we observed a relatively weak association in the analysis of CRP, which was accompanied by heterogeneity. Finally, inflammatory markers included in our analysis are the ones that have been better studied, so far, though they do not fully illustrate the complex interactions between immune function and arterial blood pressure. Thus, the interpretation of the results should be made with caution.

## CONCLUSIONS

In summary, our study shows that high levels of CRP, hs-CRP and IL-6 increase the risk of hypertension. Additional studies are needed to elucidate the potential role of these markers in the prevention and management of hypertension. Specifically, further studies should assess if levels of these inflammatory markers could be useful as a screening test to identify individuals at high risk of hypertension, and should provide a more comprehensive view of the role of immune function on the development of hypertension.

### Key messages

**What is already known on this subject?**

- Recent studies suggest that systemic inflammation may play a role in the pathogenesis and progression of hypertension. However, existing evidence is inconsistent.

**What might this study add?**

- This meta-analysis of prospective and retrospective cohort studies demonstrated that higher levels of circulating inflammation markers including C reactive protein (CRP), high-sensitivity CRP and IL-6, but not IL-1β, were associated with an increased risk of developing hypertension. In the analysis of CRP, the association did not change when the analysis was restricted only to studies that controlled for body mass index. A non-linear dose-response meta-analysis demonstrated that the risk of hypertension increased significantly and linearly with increasing circulating CRP, even within the low-risk (<1 mg/L) and intermediate-risk (1–3 mg/L) categories.

**How might this impact on clinical practice?**

- Further studies should assess if levels of these inflammatory markers could be useful as a screening test to identify individuals at high risk of hypertension.

**Contributors** AJ designed the research, screened articles, extracted and analysed data, and wrote the paper; MSZ screened articles, extracted data and wrote the paper; KR, LEB and MN critically revised the manuscript and contributed to the interpretation of the results; SS-B wrote paper, revised the manuscript, and had primary responsibility for the final content.

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**Patient consent** Not required.

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