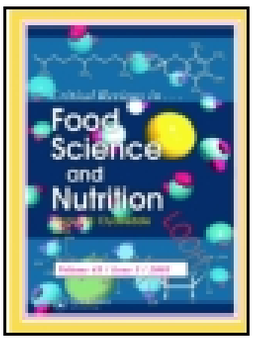

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# Famine exposure during early life and risk of hypertension in adulthood: a meta-analysis

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# Famine exposure during early life and risk of hypertension in adulthood: a meta-analysis

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**Abstract**

**Background** Many epidemiologic studies have explored the association between famine exposure and the risk of hypertension, but the results remain controversial.

**Objective** A meta-analysis was performed to determine the association between early life famine exposure, fetal famine exposure, and childhood famine exposure and risk of hypertension.

**Methods** A literature search was performed in PubMed, Web of science, Embase and China National Knowledge Infrastructure for relevant articles published up to October 2016. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model.

**Results** Sixteen studies from 14 articles for early life famine exposure, 11 studies from 10 articles for fetal famine exposure and 10 studies from 8 articles for childhood famine exposure were included in our meta-analysis. Compared with unexposed group, the pooled RRs were (1.26, 95% CI: 1.11-1.44), (1.27, 95% CI: 1.08-1.49) and (1.32, 95% CI: 1.15-1.52) for early life famine exposure, fetal famine exposure and childhood famine exposure, respectively. In subgroup analyses, the above-mentioned associations were consistent in cohort studies, and studies conducted in Asia.

**Conclusion** This meta-analysis confirmed the association between exposure to famine in early life and increased risk of hypertension in adulthood. Prevention of malnutrition during early life is an appropriate recommendation to prevent hypertension.

**Key words**

famine exposure; hypertension; malnutrition; meta-analysis

## 1. Introduction

The World Health Organization reported that the world prevalence of hypertension was about 22% among adult population in 2014 (WHO, 2014). It has been estimated that 29% of the world's adult population, or about 1.55 billion people will have hypertension by the year of 2025 (Kearney et al., 2005). Hypertension is one of the important risk factor for cardiovascular disease, stroke and renal disease (Chobanian et al., 2003; Faraco and Iadecola, 2013). In addition, hypertension has been identified as the leading cause of mortality and the third cause of disability adjusted life years worldwide (Ezzati et al., 2002). Therefore, it is important to explore the risk factors associated with hypertension for public health.

Several risk factors were confirmed to be associated with hypertension, such as genetic susceptibility, lifestyle, smoking, alcohol drinking, obesity, dietary or nutrition factors (Briasoulis et al., 2012; Chobanian et al., 2003; Falkner et al., 2000; Padmanabhan et al., 2015). Dietary protein intake and fruits and vegetables consumption were associated with lower blood pressure (Li et al., 2016; Rebholz et al., 2012). Historical famine periods which meant food shortages and nutrition deprivation might also have an influence on the risk of hypertension. A number of studies proposed that malnutrition during early life might result in permanent adaptive responses. These responses might alter organ growth, structure, physiology, which might increase the risk of chronic diseases including coronary heart disease, type 2 diabetes, and hypertension in adulthood (Alexander, 2006; Barker et al., 2006; Gluckman et al., 2008; Godfrey and Barker, 2000).

Accordingly, numerous epidemiologic studies have been performed to explore the relationship between exposure to famine during early life and the risk of hypertension in adulthood. However, the results are inconsistent. Some studies suggested significant association between famine exposure during early life and increased risk of hypertension in adulthood (Hult et al., 2010; Li et al., 2011; Wang et al., 2015; Yu et al., 2017), whereas several studies indicated no

significant association between famine exposure during early life and adult hypertension risk (Koupil et al., 2007; Woo et al., 2010). Therefore, we systematically conducted a meta-analysis to: (1) further explore the effect of famine exposure during early life on the risk of hypertension in adulthood; (2) further investigate the associations between adult hypertension risk and fetal exposure to famine and childhood exposure to famine, respectively.

## 2. Materials and methods

Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were consulted in this analysis (Moher et al., 2010).

### 2.1. Literature search strategy

We conducted a literature search to identify relevant available articles published in English or Chinese from PubMed, Web of Science, Embase and Chinese National Knowledge Infrastructure (CNKI) up to October 2016. Search terms included “famine” (or “starvation” or “hunger” or “undernutrition” or “undernourishment” or “malnutrition” or “malnourishment”) and “hypertension” (or “blood pressure”). We also reviewed the reference lists from the included articles to search for further relevant studies.

### 2.2. Inclusion criteria

The inclusion criteria were as follows: (1) an observational study published as an original article; (2) the exposure of interest was famine (The early life famine exposure was defined as the youngest exposed group in the original article); (3) the outcome of interest was hypertension; (4) relative risks (RRs), odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs) were provided; (5) the most recent and complete study was selected if data from the same population had been published more than once.

Two investigators reviewed all studies independently. If the two investigators disagreed with eligibility of an article, they discussed it with a third investigator to resolve it.

**2.3. Data extraction**

The following information was extracted from each study by two investigators independently: (1) the first author's name; (2) publication year; (3) study region; (4) age range or mean age; (5) study design; (6) sample size and number of cases; (7) definition of hypertension; (8) famine duration periods and the causes of famine; (9) famine exposure; (10) RR (we presented all results as RR for simplicity) with 95% CI; and (11) variables adjusted for in each study. Besides, RR adjusted with the most confounders was extracted.

**2.4. Statistical analyses**

Pooled measure was calculated as the inverse variance-weighted mean of the logarithm of RR with corresponding 95% CI to assess the strength of association between famine exposure and the risk of hypertension. The DerSirmonian and Laird random effect model (REM) was adopted as the pooling method (Higgins et al., 2003). $I^2$ was used to assess heterogeneity between studies ($I^2$ values of 0%, 25%, 50%, and 75% represent no, low, moderate and high heterogeneity, respectively) (Higgins and Thompson, 2002). Meta-regression with restricted maximum likelihood estimation was used to explore the potentially important covariates that might exert substantial impacts on sources of between-study heterogeneity. The leave-one-out sensitivity analysis was carried out to evaluate the key studies with substantial impact on the between-study heterogeneity (Patsopoulos et al., 2008). The influence analysis was performed to assess whether the results could have been affected markedly by a single study. Small-study effect was assessed with visual inspection of the funnel plot and Egger's test (Egger et al., 1997). All statistical analyses were performed with StataV.12.0 (Stata Corp, College Station, Texas, USA). All reported probabilities (*P*-values) were two-sided, and *P*-values less than 0.05 were considered statistically significant.

## 3. Results

### 3.1. Literature search and study characteristics

The search strategy identified 5076 articles from PubMed, 1938 articles from Web of Science, 3008 articles from Embase and 7 arcicles from Chinese National Knowledge Infrastructure. Two additional articles were found in the reference lists from included articles. After reviewing the titles or abstracts, 127 articles were retrieved. One hundred and thirteen articles were subsequently excluded for various reasons after reviewing the full text. Finally, 14 articles (Bercovich et al., 2014; Carroll et al., 2012; Chen et al., 2014; Chen et al., 2016; Hult et al., 2010; Keinan-Boker et al., 2015; Koupil et al., 2007; Li et al., 2011; Stein et al., 2006; Wang et al., 2012; Wang et al., 2015; Wang et al., 2016; Woo et al., 2010; Yu et al., 2017) including 16 studies were eligible for this meta-analysis. The flow diagram of the literature search is shown in figure 1.

A total of 16 studies from 14 articles (Bercovich et al., 2014; Carroll et al., 2012; Chen et al., 2014; Chen et al., 2016; Hult et al., 2010; Keinan-Boker et al., 2015; Koupil et al., 2007; Li et al., 2011; Stein et al., 2006; Wang et al., 2012; Wang et al., 2015; Wang et al., 2016; Woo et al., 2010; Yu et al., 2017) were included in the present meta-analysis. In these included studies, 11 studies were cross-sectional studies (Bercovich et al., 2014; Chen et al., 2016; Keinan-Boker et al., 2015; Koupil et al., 2007; Li et al., 2011; Wang et al., 2015; Wang et al., 2016; Woo et al., 2010; Yu et al., 2017) and the other 5 studies were cohort studies (Carroll et al., 2012; Chen et al., 2014; Hult et al., 2010; Stein et al., 2006; Wang et al., 2012). With regard to study region, 11 studies were conducted in Asia (Bercovich et al., 2014; Chen et al., 2014; Chen et al., 2016; Keinan-Boker et al., 2015; Li et al., 2011; Wang et al., 2012; Wang et al., 2015; Wang et al., 2016; Woo et al., 2010; Yu et al., 2017), 4 studies in Europe (Carroll et al., 2012; Koupil et al., 2007; Stein et al., 2006) and one study in Africa (Hult et al., 2010). The detailed characteristics of the included studies are shown in table 1.

### 3.2. Quantitative synthesis

#### 3.2.1. Early life famine exposure and risk of hypertension

Sixteen studies from 14 articles (Bercovich et al., 2014; Carroll et al., 2012; Chen et al., 2014; Chen et al., 2016; Hult et al., 2010; Keinan-Boker et al., 2015; Koupil et al., 2007; Li et al., 2011; Stein et al., 2006; Wang et al., 2012; Wang et al., 2015; Wang et al., 2016; Woo et al., 2010; Yu et al., 2017) with 33029 participants and 8656 cases evaluated the association between early life famine exposure and the risk of hypertension. Among the 16 studies, 6 studies showed a positive association, while the other 10 studies reported no relation between them. The pooled RR of hypertension for the exposed versus no-exposed of famine was 1.26 (95% CI: 1.11-1.44; $I^2$ = 65.0%; $P_Q$ < 0.001) (figure 2).

In subgroup analysis with study design, the pooled RRs for cohort and cross-sectional studies were 1.37 (95% CI: 1.04-1.80) and 1.22 (95%CI: 1.05-1.41), respectively. In subgroup analysis stratified by study region, the pooled RRs were 1.23 (95% CI: 1.08-1.40) and 1.10 (95% CI: 0.93-1.30) for the studies conducted in Asia and Europe, respectively. The detailed results of subgroup analyses are summarized in table 2.

#### 3.2.2. Fetal famine exposure and risk of hypertension

Ten articles (Carroll et al., 2012; Chen et al., 2014; Chen et al., 2016; Hult et al., 2010; Li et al., 2011; Stein et al., 2006; Wang et al., 2012; Wang et al., 2015; Wang et al., 2016; Yu et al., 2017) including 11 studies with 26913 participants and 6009 cases assessed the association between fetal exposure to famine and the risk of hypertension in adults. Among these studies, four studies revealed a statistically significant association, whereas the others showed no statistically significant association. The pooled RR was 1.27 (95% CI: 1.08-1.49; $I^2$ = 68.1%; $P_Q$ = 0.001) (figure S1). In subgroup analysis with study design, the positive association was significant in cohort studies (RR = 1.37, 95% CI: 1.04-1.80) but not in cross-sectional studies (RR = 1.20, 95% CI: 0.98-1.46). In subgroup analysis stratified by study

region, the positive association was significant in Asia (RR = 1.19; 95% CI: 1.04-1.36) but not in Europe (RR = 1.12, 95% CI: 0.93-1.35).

### 3.2.3. Childhood famine exposure and risk of hypertension

Ten studies from 8 articles (Chen et al., 2014; Hult et al., 2010; Koupil et al., 2007; Li et al., 2011; Wang et al., 2015; Wang et al., 2016; Woo et al., 2010; Yu et al., 2017) with 18478 participants and 5168 cases were included in childhood exposure meta-analysis. The pooled RR indicated childhood famine exposure increased the risk of hypertension in adulthood (RR = 1.32; 95% CI: 1.15-1.52; $I^2$ = 42.4%; $P_Q$ = 0.075) (figure S2). Significant association was found in subgroup analysis stratified by study design [cross-sectional studies: 1.26 (1.09-1.47) and cohort studies: 1.57 (1.24-1.99)]. When stratified by study region, the pooled RR was significant in Asia (RR = 1.33; 95% CI: 1.14-1.55) but not in Europe (RR = 1.02, 95% CI: 0.71-1.46).

### 3.4. Meta-regression and sensitivity analysis

Univariate meta-regression with covariates was conducted to explore the source of heterogeneity. In analysis of hypertension risk and early life exposure, *P* values from univariate meta-regression with the covariates of sample size, publication year, continent, study design, adjustment status of age, smoking, BMI and drinking were 0.248, 0.908, 0.187, 0.746, 0.194, 0.222, 0.299, 0.222, respectively. The findings demonstrated that no covariate conferred a significant impact on between-study heterogeneity. To further explore the potential source of heterogeneity, we also conducted the leave-one-out sensitivity analysis. The studies (Hult et al., 2010; Wang et al., 2015) conducted by Hult et al. (2010) and Wang et al. (2015) were found to contribute to between-study heterogeneity in the analysis of early life famine exposure and the risk of hypertension. After excluding these two studies, the heterogeneity was decreased ($I^2$ = 33.9%; $P_Q$ = 0.104) and the result remained significant (RR = 1.16; 95% CI: 1.05-1.28).

In analysis of hypertension risk and fetal exposure, the corresponding *P* values from univariate meta-analysis were 0.405, 0.435, 0.072, 0.534, 0.477, 0.712, 0.591, 0.712, respectively. Results from leave-one-out sensitivity analysis found that the study (Hult et al., 2010) conducted by Hult et al. (2010) contributed to between-study heterogeneity. After excluding this study, the heterogeneity decreased to 34.4% ($P_Q$ = 0.133) and the pooled RR was 1.18 (1.05-1.31).

In the analysis of childhood exposure to famine and hypertension risk, the corresponding *P* values from univariate meta-analysis were 0.624, 0.117, 0.696, 0.215, 0.143 0.253, 0.014, 0.253, respectively. BMI adjustment status was found to contribute to between-study heterogeneity (P = 0.014).

### 3.6. Influence analysis and small-study effect

Influence analysis found that one study (Woo et al., 2010) conducted by Woo et al. (2010) had an excessive influence on the pooled RR between childhood famine exposure and hypertension risk. After excluding this study, the association was remained significant (RR = 1.42; 95% CI: 1.26-1.58, $I^2$ = 0%, $P_Q$ = 0.659). No individual study had excessive influence on the pooled effect between hypertension risk and early life exposure and fetal exposure, respectively.

The funnel plot and Egger's test showed no evidence of significant small-study effect for the analysis between hypertension risk and early life famine exposure (P = 0.108, figure3), fetal famine exposure (P = 0.245, figure S3) and childhood famine exposure (P = 0.274, figure S4), respectively.

## 4. Discussion

This meta-analysis evaluated the association between famine exposure and the risk of hypertension. The results suggested the positive association between exposure to famine during early life and risk of adult hypertension. We also found that both fetal exposure and childhood exposure were associated with a significant increase in the risk of hypertension. In subgroup analyses by study design and study region, the positive associations between hypertension

risk and early life famine exposure, fetal famine exposure and childhood famine exposure were observed in cohort studies and studies conducted in Asia.

The mechanisms of famine exposure during early life and the risk of hypertension in adulthood are still not clear now. Nevertheless, several plausible biological explanations have been reported. (1) The thrifty phenotype hypothesis (Hales and Barker, 2001) suggested that fetal malnutrition might induce physiological and/or metabolic adaptations to ensure nutrient supply to the most vital ones (e.g., brain) at the expense of the less vital ones (e.g., nephron cell mass). Such fetal adaptations may increase the chance of survival in poor nutrition environment, but impaired metabolic functional capacity in coping with metabolic stressors in postnatal life, which increased the risk of chronic diseases (e.g., hypertension). (2) The epigenetic explanation (Jirtle and Skinner, 2007; Tobi et al., 2009) indicated that adverse environment exposure in early life may alter gene expression and change phenotype in part by impinging on and modifying the epigenome, which can potentially change disease susceptibility in later life. (3) If the prenatal and postnatal environments match, the physiological settings achieved through the processes of developmental plasticity will leave the organism well prepared for the postnatal environment (Gluckman and Hanson, 2004). For childhood famine exposure, a mismatch between the prenatal and postnatal environments may be pathogenic, which might elevate the risk of hypertension. All the above reasons could increase the risk of hypertension in adults with famine exposure.

Between-study heterogeneity is common in meta-analysis studies (Munafo and Flint, 2004) and it is essential to explore the potential sources of between-study heterogeneity. In this meta-analysis, low and moderate heterogeneities were found. Univariate meta-regression with covariates of sample size, publication year, study region, study design, and whether the RR (95%CI) was adjusted for age, smoking, sex, BMI and drinking were carried out. In the analysis of childhood exposure to famine and hypertension risk, BMI adjustment status was found to contribute to between-study heterogeneity. The proportion of between-study heterogeneity explained by BMI adjustment status was 100%. The

heterogeneity decreased to 0% among studies adjusted for BMI. However, meta-regression did not find the source of between-study heterogeneities in analyses of hypertension risk and early life exposure and fetal exposure, respectively. Presumably, difference in the severity of famine exposure, duration of famine exposure, adjusted for covariates, the definition of hypertension or other unknown confounding factor, may be an important determinant in the heterogeneity. We also conducted leave-one-out sensitivity analysis to reduce the heterogeneity. Two studies (Hult et al., 2010; Wang et al., 2015) conducted by Hult et al. (2010) and Wang et al. (2015) were found to contribute to between-study heterogeneity for early life famine exposure, and one study (Hult et al., 2010) conducted by Hult et al. (2010) was found to contribute to between-study heterogeneity for fetal famine exposure. The result remained significant after reducing the heterogeneity in the analysis of early life famine exposure and hypertension risk, and fetal famine exposure and hypertension risk. These results proved that our results were stable and credible. The heterogeneity caused by Hult et al.'s study may lie in the participants who come from Africa, but other studies come from Asia or Europe. The difference of social and economic status had great effects on the nutrition status and hypertension. Moreover, this study only adjusted for BMI, but ignored the influence of other important confounding factors (e.g., age). For the study conducted by Wang et al. (2015), it adjusted more confounding factors than any other studies, and the mean age gap between case and control group was larger than other studies. In influence analysis, one study (Woo et al., 2010) conducted by Woo et al (2010) had excessive influence on the pooled RR between childhood famine exposure and hypertension risk. After excluding this study, the association remained significant. The study conducted by Woo et al (2010) had no definite famine duration time, and participants were classified as famine exposed group if they had experienced caloric restriction for a continuous period of at least one year during their period. Besides, famine exposure was attained by questionnaire, not by birth date or region like other ten studies, so recall bias might exist in this study.

This meta-analysis has several strengths. Firstly, our meta-analysis enlarged sample size compared with original individual study, enhancing statistical power to provide more precise and reliable results. Secondly, no substantially

change in relationship between famine exposure and hypertension risk was found in sensitivity analysis. Therefore, the results were more reasonable and convincing. Thirdly, considering the potential differences of famine exposure in fetal period and childhood period, we further assessed the effects of these two periods of famine exposure on the risk of hypertension.

However, several potential limitations in our study should be considered. Firstly, the degree of famine exposure was not provided in original article. Thus, we could not analysis the severity of famine exposure and the risk of hypertension. Secondly, the measurement of BP was different in original studies, ie, reported by participants or measured by investigators. Thirdly, the age of case and control group was not matched in most of original articles, the results might be influenced by this factor to some extent. Fourthly, residual confounding (e.g., salt intake) could not be thoroughly estimated and the confounders adjusted for varied among studies, which might affect the results. Fifthly, this meta-analysis includes only observational studies. The association detected in observational studies can be affected by many factors (e.g., variations in exposure and outcome definitions, selection bias, confounders). Lastly, we were unable to explore the dose-response relationship between famine exposure duration periods and hypertension because of the limited data.

**5. Conclusion**

In summary, results from this study confirmed the association between exposure to famine in early life and increased risk of hypertension in adulthood. This meta-analysis indicates that early life nutrition is critical for the risk of hypertension in late life. Therefore, we should pay much attention to the prevention of malnutrition during early life for reducing hypertension risk. More well-designed cohort studies are needed to confirmed the conclusion.

**Conflict of interest disclosure**

We declare that we have no conflict of finical and commercial interest.

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Table 1. Characteristics of included studies for famine exposure and the risk of hypertension

| Author | Continent (year) | Study design | Age range/ mean age (case/control) | Participants (cases) | Exposure | RR (95% CI) | Famine duration periods | Definition of outcome | Adjustment for covariates |
|---|---|---|---|---|---|---|---|---|---|
| Yu et al | Asia (2017) | CS | 53.0/50.3<br>51.6/50.3 | 2438 (884)<br>3159 (1248) | Fetal exposed | 1.24 (1.01-1.51) | 1959-1961[1] | Self-reported physician diagnosed hypertension, use of antihypertensive medication, and SBP ≥ 140 mmHg or DBP ≥ 90 mmHg | Sex, education, smoking status, drinking status, physical activity, family history of hypertension, fruit intake, vegetable intake, BMI, central obesity, and famine severity |
| | | | | | Early-child exposed | 1.44 (1.20-1.73) | | | |
| Wang et al | Asia (2016) | CS | 50.4/46.8<br>54.3/46.8 | 1171 (232)<br>960 (219) | Fetal exposed | 0.92 (0.45-1.88) | 1959-1961[1] | Previous diagnosis of hypertension, or regular use of anti-hypertensive medication, or DBP ≥90 mmHg or SBP ≥140 mmHg | BMI, sex, smoking and drinking |
| | | | | | Early-child exposed | 1.33 (0.84-2.14) | | | |
| Chen et al | Asia (2016) | CS | 49.9 (mean) | 7903 (2060) | Fetal exposed | 1.02 (0.86-1.22) | 1959-1961[1] | Previous diagnosis of hypertension, or current use of anti-hypertensive medication, or SBP≥ 140mmHg and/or DBP ≥ 90mmHg | Age |
| Wang et al | Asia (2015) | CS | 47.0/40.9<br>51.6/40.9 | 3268 (506)<br>4053 (754) | Fetal exposed | 1.60 (1.21-2.11) | 1959-1961[1] | previous diagnosis of hypertension, or use of anti-hypertensive medication, or SBP≥ 140mmHg or | Age, sex, regional, income, education, family history of hypertension, smoking, drinking, uric acid, BMI, type |
| | | | | | Childhood exposed | 1.53 (1.06-2.21) | | | |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | DBP ≥ 90mmHg | 2 diabetes, and waist circumference abnormal liver function, hyperlipidemia |
| Keinan-Boker et al | Asia (2015) | CS | 69.4/69.2 | 1086 (670) | Exposed | 1.52 (1.17-1.99) | 1940-1945[2] | A physician's diagnoses, oral medications | Age, gender, BMI and dyslipidemia |
| Bercovich et al | Asia (2014) | CS | NA | 300 (43) | Exposed | 2.20 (1.20-3.8) | 1940-1945[2] | Self-reported | Gender and BMI |
| Chen et al | Asia (2014) | Cohort | 49.2/46.1<br>52.0/46.1 | 944 (226)<br>1094 (279) | Fetal exposed | 1.24 (0.90-1.73) | 1959-1961[1] | presence or not from any of diagnosis of hypertension, taking anti-hypertension drugs, or SBP≥ 140mmHg and DBP ≥ 90mmHg | Age, marital status, BMI, smoke, waist circumference, and alcohol use |
| | | | | | Early-child exposed | 1.48 (1.11-1.98) | | | |
| Wang et al | Asia (2012) | Cohort | 46-53 | 6028 (683) | Fetal exposed | 1.16 (0.95-1.42) | 1959-1961[1] | Previous diagnosis of hypertension, or current use of anti-hypertensive medication, or SBP≥ 140mmHg or DBP ≥ 90mmHg | Age, education, occupations, smoking, alcohol, physical activity, BMI, short stature, preference for salty foods, residence in urban areas |
| Carroll et al | Europe (2012) | Cohort | 58.2 (mean) | 453 (218) | Fetal exposed | 1.05 (0.84-1.31) | 1944-1945[2] | Self-reported | Age, sex, BMI, baseline SBP, socio-economic status, hypertensive medication, peak SBP reactivity, task |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | involvement |
| Li et al | Asia (2011) | CS | 42.0/ 39.0 | 1791 (313) (Less) | Fetal exposed | 0.86 (0.57-1.30) | 1959-1961[1] | Previous diagnosis of hypertension, or current use of anti-hypertensive medication, or SBP≥ 140mmHg or DBP ≥ 90mmHg | Sex, family income, educational level, smoking, alcohol use, physical activity level, dietary intake of salt, calcium, fat, red meat, fruit and vegetable, BMI and family history of hypertension |
| | | | | 2133 (435) | Early-child exposed | 1.26 (0.88-1.81) | | | |
| | | | 45.0/39.0 | 1168 (171) (Severely) | Fetal exposed | 1.88 (1.00-3.53) | | | |
| | | | | 1475 (256) | Early-child exposed | 1.74 (1.04-2.89) | | | |
| Woo et al | Asia (2010) | CS | ≥65 | 3732 (1586) | Childhood exposed | 1.04 (0.89-1.22) | ≥1 year[1] | Self-reported | Age, sex, alcohol, max income, education, smoking, physical activity |
| Hult et al | Africa (2010) | Cohort | 40.5/37.0 | 778 (116) | Fetal-infant exposed | 2..87 (1.90-4.34) | 1967-1970[2] | SBP≥ 140mmHg or DBP ≥ 90mmHg, or who had a normal blood pressure but were pharmacologically treated for hypertension | BMI |
| | | | 43.0/37.0 | 874 (107) | Childhood exposed | 1.77 (1.17-2.68) | | | |
| Stein et al | Europe (2006) | Cohort | 59.0 | 971 (600) | Fetal exposed | 1.32 (0.94-1.84) | 1944-1945[2] | SBP≥ 140mmHg or DBP ≥ 90mmHg, or a history of hypertension, regardless of present blood pressure level or current medication use | Age, sex, smoking, height, alcohol, waist circumference |

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|---|---|---|---|---|---|---|---|---|---|
| Koupil et al | Europe (2007) | CS | Men 41.2/41.1 | 683 (190) | Childhood exposed | 0.97 (0.64-1.48) | 1941-1944[2] | Systolic hypertension was defined as SBP of 160+ mm Hg and diastolic hypertension as DBP of 95+ mm Hg | Age, education, occupation, ethnic group/nationality, marital status, BMI, smoking, and alcohol consumption. |
| | | | Women 40.5/37.0 | 315 (58) | Childhood exposed | 1.18 (0.59-2.36) | | | |

[1] Natural disaster; [2] War; BMI: body mass index; CS: cross-sectional; CI: confidence interval; DBP: diastolic blood pressure; NA: not available RR: relative risk; SBP: systolic blood pressure.

Table 2. Summary risk estimates of the association between famine exposure and hypertension risk

| Exposure | Subgroup | Number of studies | RR (95% CI) | Heterogeneity | |
|---|---|---|---|---|---|
| | | | | $I^2$ (%) | $P_Q$ value |
| Early life famine exposure | All studies | 16 | 1.26 (1.11-1.44) | 65.0 | < 0.001 |
| | Study design | | | | |
| | Cross-sectional | 11 | 1.22 (1.05-1.41) | 57.3 | 0.009 |
| | Cohort | 5 | 1.37 (1.04-1.80) | 78.5 | 0.001 |
| | Continent | | | | |
| | Asia | 11 | 1.23 (1.08-1.40) | 56.1 | 0.012 |
| | Europe | 4 | 1.10 (0.93-1.30) | 0 | 0.635 |
| | Africa | 1 | 2.87 (1.90-4.34) | — | — |
| | Causes of famine | | | | |
| | Natural disaster | 9 | 1.16 (1.03-1.30) | 42.7 | 0.083 |
| | War | 7 | 1.45 (1.10-1.92) | 74.9 | 0.001 |
| | Adjustment for age | | | | |
| | Yes | 10 | 1.50 (1.03-2.21) | 78.2 | < 0.001 |
| | No | 6 | 1.17 (1.06-1.31) | 65.0 | < 0.001 |
| | Adjustment for smoking | | | | |
| | Yes | 11 | 1.18 (1.06-1.32) | 25.8 | 0.198 |
| | No | 5 | 1.51 (1.07-2.13) | 86.1 | < 0.001 |
| | Adjustment for drinking | | | | |
| | Yes | 11 | 1.18 (1.06-1.32) | 25.8 | 0.198 |
| | No | 5 | 1.51 (1.07-2.13) | 86.1 | < 0.001 |
| Fetal | All studies | 11 | 1.27 (1.08-1.49) | 68.1 | 0.001 |

| | | | | | |
|---|---|---|---|---|---|
| famine exposure | Study design | | | | |
| | Cross-sectional | 6 | 1.20 (0.98-1.46) | 58.9 | 0.003 |
| | Cohort | 5 | 1.37 (1.04-1.80) | 78.5 | 0.001 |
| | Continent | | | | |
| | Asia | 8 | 1.19 (1.04-1.36) | 43.0 | 0.092 |
| | Europe | 2 | 1.12(0.93-1.35) | 21.5 | 0.259 |
| | Africa | 1 | 2.87 (1.90-4.34) | — | — |
| | Causes of famine | | | | |
| | Natural disaster | 8 | 1.19 (1.04-1.36) | 43.0 | 0.092 |
| | War | 3 | 1.55 (0.90-2.67) | 88.7 | < 0.001 |
| | Adjustment for age | | | | |
| | Yes | 5 | 1.41 (0.92-2.15) | 80.2 | < 0.001 |
| | No | 6 | 1.18 (1.04-1.35) | 42.0 | 0.125 |
| | Adjustment for smoking | | | | |
| | Yes | 8 | 1.25 (1.10-1.42) | 23.4 | 0.243 |
| | No | 3 | 1.40 (0.87-2.23) | 90.6 | < 0.001 |
| | Adjustment for drinking | | | | |
| | Yes | 8 | 1.25 (1.10-1.42) | 23.4 | 0.243 |
| | No | 3 | 1.40 (0.87-2.23) | 90.6 | < 0.001 |
| Childhood famine exposure | All studies | 10 | 1.32 (1.15-1.52) | 42.4 | 0.075 |
| | Study design | | | | |
| | Cross-sectional | 8 | 1.26 (1.09-1.47) | 40.2 | 0.111 |
| | Cohort | 2 | 1.57 (1.24-1.99) | 0.0 | 0.488 |
| | Continent | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | Asia | 7 | 1.33 (1.14-1.55) | 48.0 | 0.073 |
| | Europe | 2 | 1.02 (0.71-1.46) | 0.0 | 0.635 |
| | Africa | 1 | 1.77 (1.17-2.68) | - | - |
| | Causes of famine | | | | |
| | Natural disaster | 7 | 1.33 (1.14-1.55) | 48.0 | 0.073 |
| | War | 3 | 1.28 (0.86-1.92) | 57.0 | 0.130 |
| | Adjustment for age | | | | |
| | Yes | 5 | 1.21 (0.99-1.48) | 46.2 | 0.114 |
| | No | 5 | 1.45 (1.27-1.67) | 0.0 | 0.718 |

RR: relative risk; CI: confidence interval.

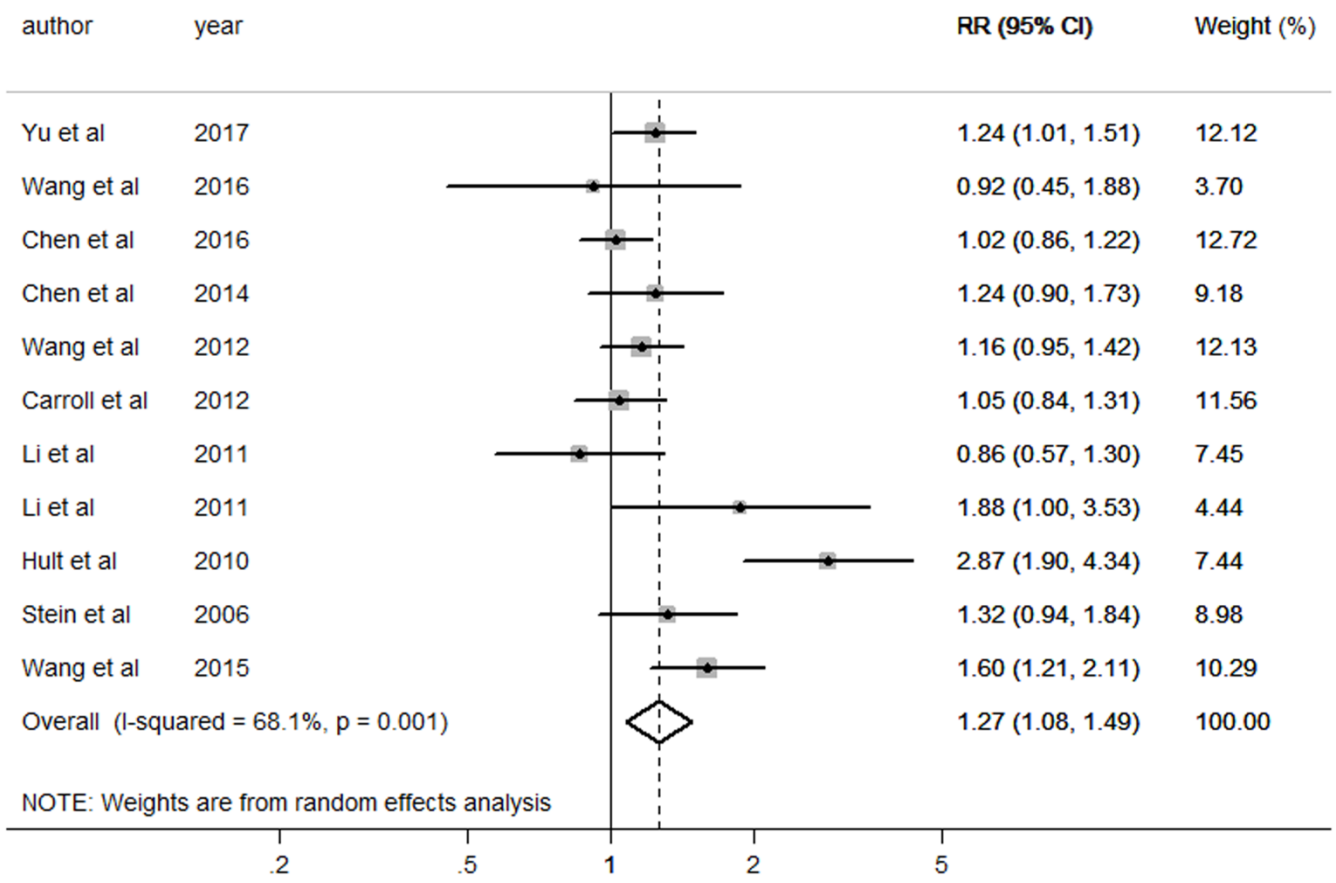


Figure 1. Flow chart of the selection of studies included in the meta-analysis. RR, relative risk; CI: confidence interval.

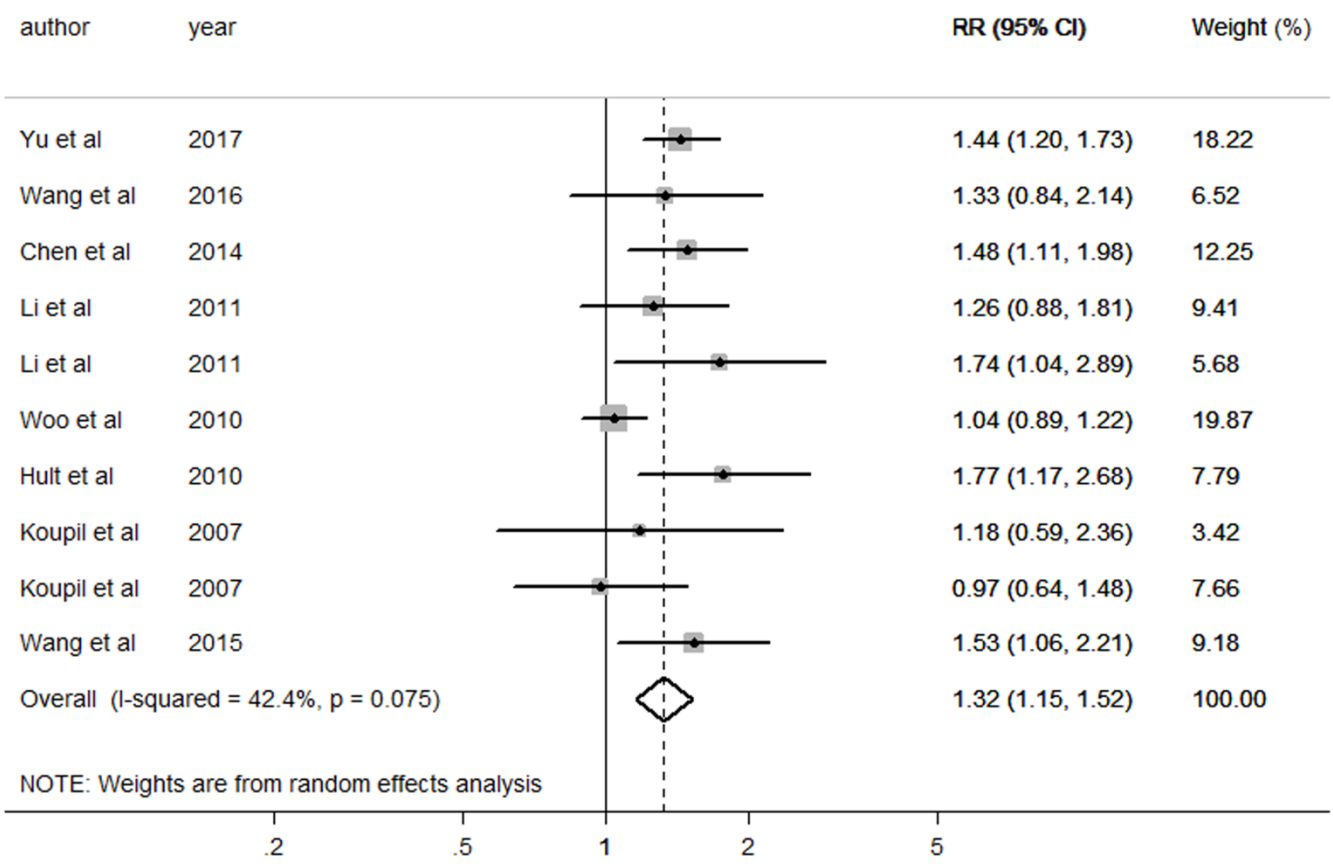


Figure 2. Forest plot of early life famine exposure and the risk of hypertension. The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% confidence intervals. RR, relative risk; CI: confidence interval.

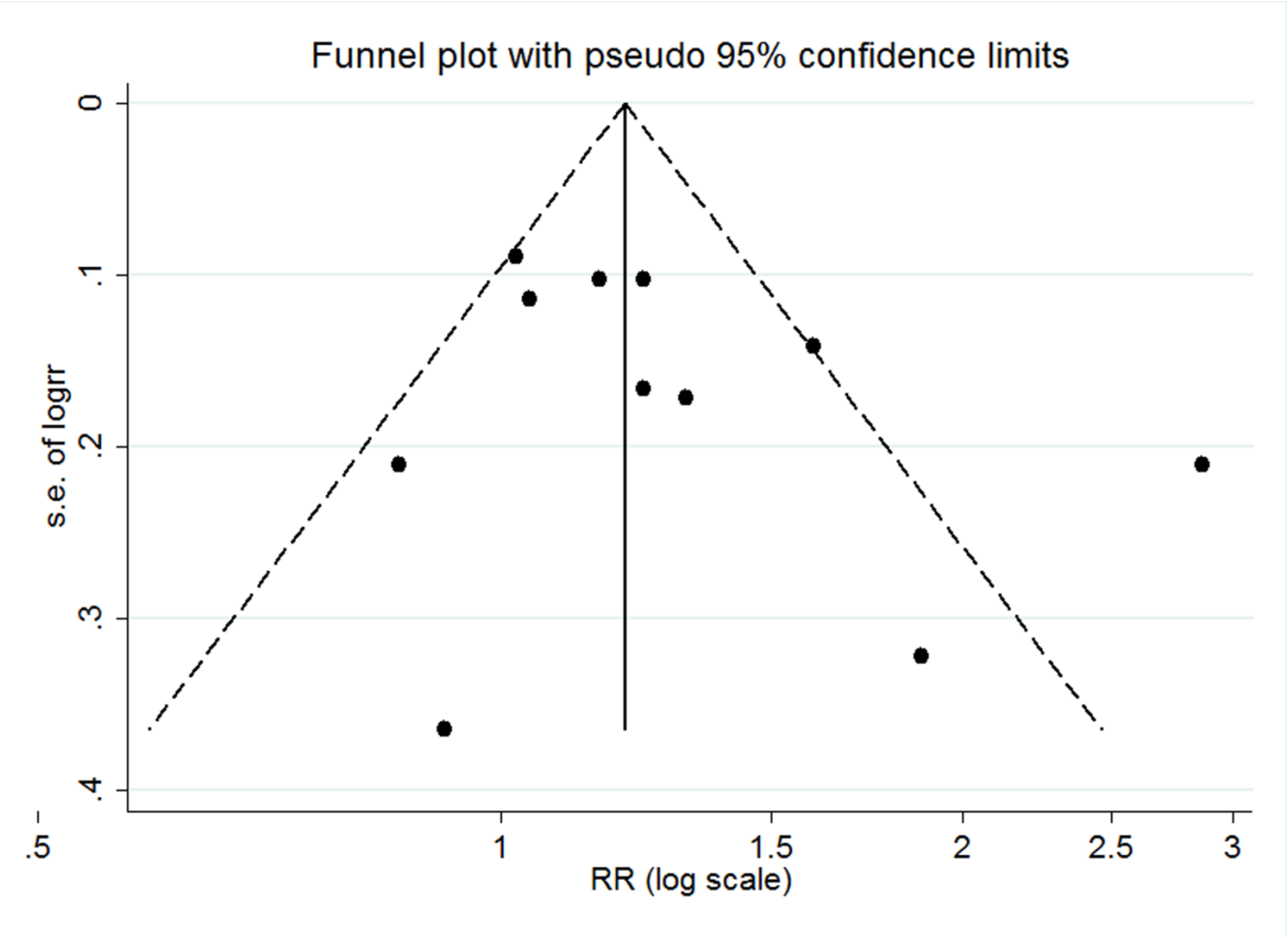


Figure 3. Funnel plot with pseudo 95% confidence limits for the analysis of early life famine exposure and risk of hypertension. RR, relative risk.