Abstract

Background
Hypertension is a leading global health threat and a major cardiovascular disease. Since clinical interventions are effective in delaying the disease progression from prehypertension to hypertension, diagnostic prediction models to identify patient populations at high risk for hypertension are imperative.

Methods
Both PubMed and Embase databases were searched for eligible reports of either prediction models or risk scores of hypertension. The study data were collected, including risk factors, statistic methods, characteristics of study design and participants, performance measurement, etc.

Results
From the searched literature, 26 studies reporting 48 prediction models were selected. Among them, 20 reports studied the established models using traditional risk factors, such as body mass index (BMI), age, smoking, blood pressure (BP) level, parental history of hypertension, and biochemical factors, whereas 6 reports used genetic risk score (GRS) as the prediction factor. AUC ranged from 0.64 to 0.97, and C-statistic ranged from 60% to 90%.

Conclusions
The traditional models are still the predominant risk prediction models for hypertension, but recently, more models have begun to incorporate genetic factors as part of their model
predictors. However, these genetic predictors need to be well selected. The current reported models have acceptable to good discrimination and calibration ability, but whether the models can be applied in clinical practice still needs more validation and adjustment.

Introduction

The number of people living with hypertension is predicted to be 1.56 billion worldwide by the year 2025[1]. In addition, hypertension contributes to ~13% of the total mortality worldwide[2] and ~7% of the total disability-adjusted life years, creating a tremendous financial burden for both patients and the health-care system[2]. The association between hypertension and traditional risk factors such as age, body mass index (BMI), blood pressure (BP), smoking and family history have been well studied, whereas the roles of genetic variants associated with the incidence of hypertension are less clearly defined[3,4].

In 2013, Echouffo-Tcheugui JB et al. published a systematic review of 11 articles with 15 models[5]. Most of these models were carried out in Caucasian populations, and the prediction factors used in these studies were almost identical. Noticeably, none of the above models took genetic factors into consideration, whereas in recent years, more study designs of hypertension risk prediction models have tended not only to have larger patient enrollment size with diverse ethnic backgrounds but also to include genetic factors in these models. Therefore, we conducted this systematic review to summarize the current development status and performance of hypertension prediction models, which would provide updates for health-care providers and policy-makers in the field of hypertension research and clinical practice. This review could also help improve hypertension awareness, identify populations at high risk for hypertension, and determine those individuals who could benefit from early interventions.

Method

Search strategy

The research strategy, study selection and analysis methods used in this study followed the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement[6] (S1 Table). We conducted a complete literature search in both PubMed and Embase to retrieve all published reports about hypertension prediction models using the keywords “hypertension”, “high blood pressure”, “prediction model”, and “risk score”. The search strategy was (((prediction model[Title/Abstract]) OR risk score)) AND ((hypertension[Title/Abstract]) OR high blood pressure[Title/Abstract]). The last search was conducted on September 5, 2016. The related references from those retrieved reports were also searched manually to identify any additional published reports. For those identified articles that were not available online, we contacted the authors directly to request copies.

Inclusion and exclusion criteria

All the retrieved reports were screened independently for inclusion by two researchers from this study. The titles and abstracts of retrieved papers were used as the primary review content for inclusion verification. However, if questioned or unclear, the full article was reviewed prior to inclusion decision. The study’s inclusion criteria include: 1. Reporting a risk assessment tool, e.g., an equation or a risk score system; 2. Predicting the risk incidence of essential hypertension; 3. Published in English-language journals; 4. Conducted in subjects 18 years old or
older; 5. Reporting quantitative measures of model performance (preferred but not necessarily required). Exclusion criteria include: 1. Studies only describe association between risk factors and incident hypertension; 2. Simulation studies; 3. Studies predict gestation-related hypertension; 4. Unpublished research data.

Data extraction and synthesis

Any discrepancy of the independently collected data from the two researchers was resolved by group discussion among all participating project investigators. The following data were extracted from each study: study design, subject characteristics, number of subjects in derivation and validation cohorts, number of subjects who developed hypertension, number of candidate variables considered, variables included in the final model and statistical method used for development of the model. We extracted the area under the curve (AUC) of the receiver operating characteristic or C-statistic to assess the discrimination ability of each model. We also collected the value of Hosmer–Lemeshow $\chi^2$, and the $p$ value of the corresponding test statistic, to assess model calibration ability. Due to the wide spread of differences in risk factors, population, study design, and sufficiency of data, it was impossible to perform meta-analysis in our current study. Instead, we opted to conduct a narrative synthesis of the evidence. However, to provide a nice summary graph, we applied the random effects model meta-analysis to combine the estimates of the AUC from studies with enough data and assessed the between-study heterogeneity, with the use of the Stata statistical software version 12.0 (http://www.stata.com/). The data used in meta-analysis was transformed in the way of double arcsine transformations to addresses the problems of confidence limits and variance instability. The potential publication bias was assessed with funnel plot, as well as Begg’s and Egger’s test. A P value < .05 indicated significant publication bias.

Results

The process of the literature search and paper selection, according to PRISMA guidelines, is presented in Fig 1. Our initial literature search resulted in 7332 citations; only 26 articles were selected, reporting 48 prediction models. Table 1 shows the characteristics of these 26 studies, of which 5 were conducted in the US[7–11], 5 in Europe[12–16], 7 in China[17–23], 4 in Korea[24–27], 2 in Japan[28,29], 2 in Iran[30,31], and 1 in India[32]. Among them, only 1 study was carried out in women alone[9]. A total of 162,358 subjects were enrolled in these studies. In the longitudinal studies, participants were followed up for 3 to 30 years. The definition of hypertension among these studies was consistent. Twenty-four studies defined hypertension as either systolic blood pressure (SBP) $\geq$ 140 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg, or the use of antihypertensive drugs. Two studies[17,31] defined isolated systolic hypertension as SBP $\geq$ 140 mmHg and DBP $\leq$ 90 mmHg, and isolated diastolic hypertension as DBP $\geq$ 90 mmHg and SBP $\leq$ 140 mmHg. Twenty studies used traditional factors only, and 6 studies[11,14,16,19,21,26] also included Genetic Risk Score (GRS) factors (indeed, 2 studies[19,26] used genetic risk factors exclusively). The common predictors included in most models were age, gender, BMI, SBP, DBP, and parental history of hypertension. The SNPs that were used for setting up the GRS system were nearly all derived from the genome-wide association study (GWAS). The number of SNPs used in these studies ranged from 2 to 32 (S2 Table). The AUC or C-statistic of models[11,21] including GRS were superior compared to those without GRS (C-index change = 0.3%–0.5%; $p<0.05$). Twelve studies proposed to build models with logistic regression, 7 with COX regression, 6 with Weibull regression, and 1 with linear regression.
Performance of prediction models

The performance of prediction models is shown in Table 2. AUC ranged from 0.64 to 0.97, and C-statistic ranged from 60% to 90%. The results of pooling 35 models in meta-analysis.
Table 1. Characteristics of included articles.

| First author          | Year | Country/Ethnicity | Study design | Outcomes/total | Age                  | Definition of hypertension                                                                 | Follow up (years) | Type of statistic               |
|-----------------------|------|-------------------|--------------|----------------|----------------------|-------------------------------------------------------------------------------------------|-------------------|--------------------------------|
| Pearson               | 1990 | USA/Mixed, mainly Whites | Prospective  | 104/1130       | 25 or less          | Self-reported use of BP lowering medications                                                | 30                | Cox regression analysis         |
| Chih-Jung Yeh         | 2001 | China/Taiwan      | Prospective  | 87/2373        | ≥20 SBP ≥ 140 mmHg and DBP < 90 mmHg                                                   | 3.23              | Cox regression analysis         |
| Nisha I. Parikh       | 2008 | American/whites   | Prospective  | 796/1717       | 20 to 69             | JNC—VII definition                                                                       | 4                 | Weibull regression model        |
| Nina P. Paynter       | 2009 | American/whites   | Prospective  | 1258/8207      | 35 to 68              | JNC—VII definition                                                                       | 5                 | Weibull regression              |
| Mika Kivimäki         | 2009 | England/whites    | Prospective  | 1029/2506      | ≥35                  | JNC—VII definition                                                                       | 6.15              | multivariate Weibull model      |
| Mohammadreza Bozorgmanesh | 2010 | Iran/Asians       | Prospective  | 805/4656       | 42                   | the average of two DBP measurements ≥ 90 mmHg or the average of two SBP ≥ 140 mmHg or taking antihypertension medication | 6                 | Cox proportional hazard regression models |
| K-L Chien             | 2011 | China/Taiwan      | Prospective  | 1029/2506      | 35 to 68              | JNC—VII definition                                                                       | 9                 | Bayesian networks               |
| Cristiano Fava        | 2013 | Sweden/whites     | Prospective  | NR/10784       | NR                   | JNC—VII definition                                                                       | 23                | Multivariate linear and logistic regression |
| Nam-Kyoo Lim          | 2013 | Korea/Asian       | Prospective  | 819/4747       | 40 to 69              | JNC—VII definition                                                                       | 4                 | Weibull regression analysis     |
| Henry                 | 2013 | Northeast Germany/whites | Prospective  | 1029/2506      | 20–79 SBP/DBP ≥ 140/90 mmHg                                                      | 5                 | generalized estimating equations method |
| Li Guoqi              | 2014 | China/Asians      | Prospective  | 177/3899       | 35–64                 | JNC—VII definition                                                                       | 15                | logistic regression             |
| Yun-Hee Choi          | 2014 | Mexican Americans | Prospective  | NR/443         | NR                   | JNC—VII definition                                                                       | nr                | logistic regression             |
| Yue Qi                | 2014 | China/Asians      | Case control  | 1009           | 38.8±8.9             | JNC—VII definition                                                                       | nr                | logistic regression             |
| Bum Ju Lee            | 2014 | Korea/Asians      | Cross-sectional | 12789         | 21–85 SBP/DBP ≥ 140/90 mmHg or physician-diagnosed hypertension                        | nr                | correlation-based feature selection |
| Nam-Kyoo Lim          | 2015 | Korea/Asian       | Prospective  | 563/2290       | 40 to 69              | JNC—VII definition                                                                       | 4                 | logistic regression             |
| Toshiaki Otsuka       | 2015 | Japan/Asians      | Prospective  | 15025          | 38.8±8.9             | JNC—VII definition                                                                       | 4                 | Cox proportional hazards model |

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The calibration was assessed by Hosmer–Lemeshow $\chi^2$, suggesting that these models had good calibration ability.

### Validation of prediction models

The prediction models of 7 studies[9,10,12,13,15,26,28] were validated in internal cohorts through split samples, with C-statistics ranging from 0.79 to 0.9. Three models were externally validated. The SHIP risk model[15] from northeast Germany was validated by data from the Danish INTER99, comprising 2887 participants, and it performed well, with an AUC of 0.77 ($P = 0.74$) and the Hosmer–Lemeshow $\chi^2$ test of 40.6 ($P = 2 \times 10^{-6}$). The KoGES risk score from Korea was externally validated by a large nationwide Korean cohort[33]. The discrimination (AUC = 0.733) and calibration (Hosmer–Lemeshow $\chi^2 = 14.85$, $P = 0.062$) of this model...
Table 2. Characteristics of prediction models.

| First author    | Year | Model name                        | Candidate variables (n) | Variables include                                                                 | AUC/C-statistic       | Calibration        | Method of validation |
|-----------------|------|-----------------------------------|-------------------------|-----------------------------------------------------------------------------------|-----------------------|--------------------|----------------------|
| Pearson         | 1990 | Johns Hopkins                     | NR                      | Age, SBP at baseline, paternal history of hypertension and BMI                     | NR                    | NR                 | NR                   |
| Chih-Jung Yeh   | 2001 | ISH risk prediction model         | NR                      | age, DM, and fibrinogen concentration in men, and age and APTT (activated partial thromboplastin time) in women | NR                    | NR                 | NR                   |
| Chih-Jung Yeh   | 2001 | IDH risk prediction model         | NR                      | elevated BMI, glucose concentration, and uric acid concentration were significant factors in men; BMI was the only significant factor in women. | NR                    | NR                 | NR                   |
| Nisha I. Parikh | 2008 | Framingham risk score             | 11                      | age, sex, SBP, DBP, BMI, parental hypertension, and cigarette smoking               | NR/0.788.95% CI (0.733, 0.803) | Hosmer–Lemeshow $\chi^2 = 4.35$ | NR                   |
| Nina P. Paynter | 2009 | WHS inclusive risk prediction     | 14                      | age, BP, BMI, total grain intake, apolipoprotein B, ethnicity, lipoprotein(a), C-reactive protein | NR/0.705              | Hosmer–Lemeshow $\chi^2 = 2.9(P = 0.94)$ | Internal validation, split-sample 2:1 |
| Nina P. Paynter | 2009 | WHS Simplified Model with Lipids  | 23                      | Age, BMI, SBP, DBP, ethnicity (Black or Hispanic) and total to HDL- cholesterol ratio | NR/0.705              | Hosmer–Lemeshow $\chi^2 = 9.4(P = 0.31)$ | Internal validation, split-sample 2:1 |
| Nina P. Paynter | 2009 | WHS Simplified Model              | 23                      | Age, BMI, race/ethnicity, SBP, and DBP                                              | NR/0.703              | Hosmer–Lemeshow $\chi^2 = 6.0(P = 0.64)$ | Internal validation, split-sample 2:1 |
| Mika Kivimäki   | 2009 | Whitehall II risk score           | NR                      | Age, sex, SBP, DBP, BMI, parental hypertension and cigarette smoking                | NR/0.80               | Hosmer–Lemeshow $\chi^2 = 11.5(<20)$ | Internal validation, split-sample (6:4) |
| Mika Kivimäki   | 2010 | Whitehall II Repeat measures risk score | NR                      | repeat measures of BP, weight and height, current cigarette smoking and parental history of hypertension | NR/0.799              | predicted-to-observed ratio 0.98, 95% CI (0.89, 1.08). Hosmer–Lemeshow $\chi^2 = 1.6$ | Internal validation, split-sample |
| Mika Kivimäki   | 2010 | the average blood pressure risk score | NR                      | average BP, weight and height, current cigarette smoking and parental history of hypertension | NR/0.794              | predicted-to-observed ratio 0.96, 95%CI (0.88, 1.06) | Internal validation, split-sample |
| Mika Kivimäki   | 2010 | the ‘usual’ blood pressure risk score | NR                      | the ‘usual’ BP, weight and height, cigarette smoking and parental history of hypertension | NR                    | NR                 | Internal validation, split-sample |
| Abhijit V. Kshirsagar | 2010 | ARIC/CHC risk score               | 11                      | Age, level of SBP or DBP, smoking, family history of hypertension, diabetes mellitus, high BMI, female sex, and lack of exercise | 0.739 (3years), 0.755 (6 years), 0.800 (9 years) and 0.782 (ever)/nr | NR                   | Internal validation, split-sample |

(Continued)
| First author                | Year      | Model name                        | Candidate variables (n) | Variables include                                                                 | AUC/C-statistic                        | Calibration                          | Method of validation |
|-----------------------------|-----------|-----------------------------------|-------------------------|----------------------------------------------------------------------------------|----------------------------------------|--------------------------------------|----------------------|
| Mohammadreza Bozorgmanesh   | 2011      | TLGS risk multivariable models     | NR                     | for women: age, waist circumference, DBP, SBP, and family history of premature CVD; for men: age, DBP, SBP, and smoking; for both: the interaction terms between age and SBP, Increasing levels of SBP | NR(0.731 (95% CI 0.706–0.755) for women; 0.741 (95% CI 0.719–0.763) for men) | women (Hosmer–Lemeshow $\chi^2 = 7.8$, $P = 0.554$) and men (Hosmer–Lemeshow $\chi^2 = 8.8$, $P = 0.452$). | NR                                 |
| Mohammadreza Bozorgmanesh   | 2011      | TLGS risk score                   | NR                     | Waist circumference, DBP, family history of premature cardiovascular disease, daily smoking, SBP | NR(0.727 (95% CI 0.709–0.744)) | NR                                   | NR                                 |
| K-L Chien                   | 2011      | Taiwan BP clinical risk model     | NR                     | gender, age, BMI, SBP and DBP                                                    | 0.732,95% CI (0.712,0.752)/NR | Hosmer–Lemeshow $\chi^2 = 8.3$, $p = 0.40$ | NR                                 |
| K-L Chien                   | 2011      | Taiwan BP clinical risk model     | NR                     | gender, age, BMI, SBP and DBP, white blood count, fasting glucose and uric acid    | 0.735,95% CI (0.715–0.755)/NR | Hosmer–Lemeshow $\chi^2 = 13.2$, $p = 0.11$ | NR                                 |
| Cristiano Fava              | 2013      | Swedish nongenetic risk model     | NR                     | age, sex, age$^2$, sex times age, heart rate, obesity, diabetes, hypertriglyceridemia, prehypertension, family history of hypertension, sedentary in spare time, problematic alcohol behavior, married or living as a couple, high-level non-manual work, smoking | NR(0.662) | NR                                   | NR                                 |
| Cristiano Fava              | 2013      | Swedish genetic risk model        | 29                     | 29 SNPs                                                                          | NR(0.664) | NR                                   | NR                                 |
| Cristiano Fava              | 2013      | Swedish risk model 2              | NR                     | age, sex, age$^2$, sex times age, heart rate, obesity, diabetes, hypertriglyceridemia, prehypertension, family history of hypertension, sedentary in spare time, problematic alcohol behavior, married or living as a couple, high-level non-manual work, smoking, 29 SNPs | NR(0.664) | NR                                   | NR                                 |
| Nam-Kyoo Lim                | 2013      | KoGES risk score                  | NR                     | age, sex, smoking, SBP, DBP, parental hypertension, BMI                          | 0.79,95% CI (0.764,0.815)/NR | $\chi^2 = 13.42$, $P = 0.0981$ | NR                                 |
| Henry                       | 2013      | SHIP risk model                   | 42                     | age, mean arterial pressure, rs16998073, serum glucose and urinary albumin concentrations, interaction between age and serum glucose, interaction between rs16998073 and urinary albumin concentrations | training set 0.78 95% CI(0.74,0.82); validation set 0.79,95%CI (0.75,0.83)/NR | Hosmer–Lemeshow $\chi^2 = 11.82$ ($P = 0.16$) for training set; 11.65 ($P = 0.17$) for the validation set | Internal (1:1) and external validation |
| Yue Qi                      | 2014      | northeastern Han Chinese genetic risk score | 10                     | 9 SNPs                                                                           | NR                                    | NR                                   | NR                                 |

(Continued)
| First author          | Year | Model name                                           | Candidate variables (n) | Variables include                                                                 | AUC/C-statistic | Calibration | Method of validation |
|-----------------------|------|------------------------------------------------------|-------------------------|-----------------------------------------------------------------------------------|-----------------|-------------|---------------------|
| Bum Ju Lee            | 2014 | Demographic indices risk prediction model 1 for women | 41                      | Height, Age, NeckC, AxillaryC, RibC, WaistC, PelvicC, Rib_Hip, Waist_Hip, Pelvic_Hip, Rib_Pelvic, Axillary_Rib, Chest_Rib, Axillary_Chest, Forehead_Neck | 0.696 for Bayes-correlation-based feature selection; 0.713 for logistic regression-correlation-based feature selection/NR | NR           | NR                  |
| Bum Ju Lee            | 2014 | Demographic indices risk prediction model 2 for women | 41                      | Height, Age, ForeheadC, NeckC, HipC, Axillary_Hip, Axillary_Pelvic, Chest_Pelvic, Chest_Rib | 0.713/NR        | NR          | NR                  |
| Bum Ju Lee            | 2014 | Demographic indices risk prediction model 3 for women | 41                      | Height, Weight, BMI, Age, ChestC, Forehead_Hip, Waist_Hip, Chest_Pelvic, Waist_Pelvic, Axillary_Waist, Forehead_Rib, Neck_Axillary | 0.721/NR        | NR          | NR                  |
| Bum Ju Lee            | 2014 | Demographic indices risk prediction model 1 for men   | 41                      | Age, ForeheadC, NeckC, AxillaryC, ChestC, RibC, WaistC, PelvicC, HipC, Rib_Hip, Waist_Hip, Rib_Pelvic, Waist_Pelvic, Chest_Waist, Chest_Rib, Rib_Pelvic, Axillary_Rib, Chest_Rib, Forehead_Chest, Forehead_Neck | 0.64 for Bayes-correlation-based feature selection and 0.637 for logistic regression-correlation-based feature selection/nr | NR            | NR                  |
| Bum Ju Lee            | 2014 | Demographic indices risk prediction model 2 for men   | 41                      | Height, Age, ForeheadC, NeckC, AxillaryC, HipC, Rib_Pelvic, Neck_Pelvic, Waist_Pelvic, Chest_Waist, Chest_Rib, Neck_Chest, Axillary_Chest, Forehead_Neck | 0.646/NR        | NR          | NR                  |
| Bum Ju Lee            | 2014 | Demographic indices risk prediction model 3 for women | 41                      | Height, ForeheadC, NeckC, AxillaryC, RibC, PelvicC, Forehead_Hip, Chest_Hip, Rib_Hip, Pelvic_Hip, Forehead_Waist, Axillary_Waist, Rib_Waist, Neck_Rib, Axillary_Rib, Chest_Rib, Forehead_Axillary, Forehead_Neck, WHTR | 0.652/NR        | NR          | NR                  |
| Li Guoqi              | 2014 | China risk prediction model 1                        | NR                      | age, SBP, DBP, BMI and the history of parental hypertension | NR/0.7168       | Hosmer-Lemeshow $\chi^2 = 3.75$ | NR                  |
| Li Guoqi              | 2014 | China risk prediction model 2                        | NR                      | Age, SBP, DBP, BMI and the history of parental hypertension, TG, HDL-C | NR/0.7208       | Hosmer-Lemeshow $\chi^2 = 3.10$ | NR                  |
| Li Guoqi              | 2014 | China risk prediction score                          | NR                      | Age, SBP, DBP, BMI and the history of parental hypertension | NR              | NR          | NR                  |
| Yun-Hee Choi          | 2014 | marginal model                                       | NR                      | Intercept, Age, Gender, Smoke, Age*gender, Rs10510257 (AA), Rs10510257 (AG), Rs1047115 (GT) | 0.839/NR        | NR          | NR                  |

(Continued)
| First author         | Year  | Model name                             | Candidate variables (n) | Variables include                                                                 | AUC/C-statistic | Calibration | Method of validation |
|----------------------|-------|----------------------------------------|-------------------------|----------------------------------------------------------------------------------|-----------------|-------------|---------------------|
| Yun-Hee Choi         | 2014  | conditional model                      | NR                      | Intercept, Age, Gender, Smoke, Age×gender, Rs10510257 (AA), Rs10510257 (AG), Rs1047115 (GT) | 0.973/NR        | NR          | NR                  |
| Xiangfeng Lu         | 2015  | InterASIA risk prediction              | NR                      | Model1: Age, sex, and BMI; Model2: Model 1+smoking, drinking, pulse rate, and education; Model3: Model2 + SBP and DBP | NR/Model1:0.650 (0.637–0.663); Model2:0.683 (0.670–0.695);Model3:0.774 (0.763–0.785) | NR          | NR                  |
| Wenchao Zhang        | 2015  | biomarker-based risk-prediction model   | 11                      | inflammatory factor, blood viscosity factor, insulin resistance factor, blood pressure factor, and lipid resistance factor | 75.5% for men and 80.1% for women/nr | NR          | NR                  |
| Nam-Kyoo Lim         | 2015  | Korean genetic risk score              | 4                       | rs995322, rs17249754, rs1378942, rs12945290                                     | NR              | NR          | internal validation fivefold cross-validation |
| Minoru Yamakado      | 2015  | the PFAA index                         | 19                      | PFAA index 1, Leucine, Alanine, Tyrosine, asparagine, tryptophan, and Glycine; PFAA index 2, Isoleucine, Alanine, Tyrosine, phenylalanine, methionine and histidine | NR              | NR          | NR                  |
| Toshiaki Otsuka      | 2015  | Japanese risk prediction model         | NR                      | age, BMI, SBP and DBP, current smoking status, excessive alcohol intake, parental history of hypertension | NR/0.861, 95% CI (0.844, 0.877) | Hosmer–Lemeshow $\chi^2 = 15.2 P = 0.085$ in validation cohort | internal validation Split-sample (80% vs.20%) |
| Toshiaki Otsuka      | 2015  | Japanese risk score sheet              | NR                      | age, BMI, SBP and DBP, current smoking status, excessive alcohol intake and parental history of hypertension | NR/0.858, 95% CI (0.840,0.876) | Hosmer–Lemeshow $\chi^2 = 9.3 P = 0.41$ in validation cohort | internal validation Split-sample (80% vs.20%) |
| Joung-Won Lee        | 2015  | Anthropometric indices risk prediction | NR                      | BMI; WaistC; waist-to-hip ratio; waist-to-height ratio                        | NR              | NR          | NR                  |
| Samaneh Asgari       | 2015  | TLGS risk prediction for ISH            | 17                      | Age, SBP, BMI, 2 hours post-challenge plasma glucose                          | NR/0.91         | NR          | NR                  |
| Samaneh Asgari       | 2015  | TLGS risk prediction for IDH            | 17                      | Age, DBP, waist circumference, marital status, gender, HDL-C                | NR/0.76         | NR          | NR                  |
| Thirunavukkarasu     | 2016  | rural India risk score                 | 11                      | age, sex, years of schooling, daily intake of fruits or vegetables, current smoking, alcohol use, BP, prehypertension, central obesity, history of high blood glucose | 0.802, 95% CI(0.748–0.856)/NR | Hosmer–Lemeshow $P = 0.940$ | NR                  |
| Teemu J. Niiranen     | 2016  | genetic risk prediction model1         | 32                      | 32 SNPs                                                                       | NR              | NR          | NR                  |
| Teemu J. Niiranen     | 2016  | genetic risk prediction model2         | 32                      | model 1 + age + sex                                                           | NR              | NR          | NR                  |

(Continued)
were both good. The Framingham model was externally validated by 7 studies\cite{12,15,24,33–36} from different countries (S3 Table).

### Meta-analysis

Results from pooling 35 models in the meta-analysis showed that the AUC was 0.767, 95% CI (0.742, 0.792) indicating the performance of prediction models was well. Fig 2 shows the forest plots of analysis. As expected, the heterogeneity between studies (I-squared = 99.5%, Estimate of between-study variance Tau-squared = 0.0055) was significant (S1 file). Publication bias was evaluated with Funnel plot (Fig 3). The results (P>0.05) indicated no significant publication bias.

### Discussion

This systematic review summarizes the current evidence regarding risk models developed to predict incident hypertension. The prediction models could help identify individuals who are more susceptible to hypertension and prioritize the underlying risk factors that lead to the incidence of hypertension. In addition, it could also help individuals with high risk for hypertension and health-care providers to take preventive interventions earlier.

### Population of studies

Most of these models were derived from American, European or East Asian populations; only one study was carried out in India, and the other 2 were in Iran. It is perceivable that systematic underestimation or overestimation of risk may occur when applying a model constructed from one particular cohort to a distinct ethnic population with different characteristics (the selection of predictors and the genetic background). We found that most prediction models were established in developed countries, and only a few were established in developing or undeveloped countries. Thus, it is imperative to establish reliable predictive models in those

| First author  | Year | Model name | Candidate variables (n) | Variables include | AUC/C-statistic | Calibration | Method of validation |
|---------------|------|------------|--------------------------|-------------------|----------------|-------------|---------------------|
| Teemu J. Niiranen | 2016 | genetic risk prediction model3 | 32 | model 2 + smoking, diabetes, education, hypercholesterolemia, exercise and BMI | NR/0.803 | NR | NR |
| Chen, Y. | 2016 | Prediction for men | 20 | Age, BMI, SBP, DBP, gamma-glutamyl transferase, fasting blood glucose, Drinking, Age by BMI, Age by DBP | 0.761, 95% CI (0.752–0.771) | NR | NR |
| Chen, Y. | 2016 | Prediction for women | 20 | Age, BMI, SBP, DBP, fasting blood glucose, total cholesterol, neutrophil granulocyte, Drinking, Smoking | 0.753, 95% CI (0.741–0.765) | NR | NR |

NR means not reported; BP is blood pressure, SBP is systolic blood pressure and DBP is diastolic blood pressure; BMI is body mass index; AUC means the area under the receiver operating characteristic curve; CI means confidence interval; SNP is single nucleotide polymorphism; NeckC is Neck circumference; AxillaryC: Axillary circumference; RibC: Rib circumference; WaistC: Waist circumference; PelvicC: Pelvic circumference; Rib_Hip: Rib-to-pelvic circumference ratio; Waist_Hip: Waist-to-hip circumference ratio; Pelvic_Hip: Pelvic-to-hip circumference ratio; Rib_Pelvic: Rib-to-pelvic circumference ratio; Axillary_Rib: Axillary-to-rib circumference ratio; Chest_Rib: Chest-to-rib circumference ratio; Axillary_Chest: Axillary-to-chest circumference ratio; Forehead_Neck: Forehead-to-neck circumference ratio; WHtR: Waist-to-height circumference ratio.

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countries or regions to help reduce the incidence of hypertension and cardiovascular events caused by high blood pressure.

Predictors included

The most commonly used predictors include age, BMI, SBP, DBP, etc., which are easy to obtain in clinical practice. A few studies also take blood biochemistry factors or anthropometric parameters[25,27] as predictors (Table 2), which are also part of the routine lab test results in a general physical examination. The biochemistry factors used as predictors include blood glucose, triglycerides, high-density lipoprotein cholesterol (HDL-C), and fibrinogen. It has been reported that the level of blood glucose is associated with high blood pressure[37]. Triglyceride, cholesterol and HDL-C are also known to contribute to blood hyperviscosity[38] and vascular sclerosis, which could lead to the rise of the BP. Since hypertension is also
considered as a metabolic disease, the changes of blood biochemical factors could provide important and valuable information for the accuracy of certain hypertension prediction models.

It is well known that the interaction between environmental and genetic factors contributes to the development of hypertension. Theoretically, the prediction models should contain both environmental and genetic predictors. Most of the SNPs used to construct GRS were from GWAS (S2 Table). In the Finnish study[16], results showed that GRS were significantly associated with BP but weakly associated with BP increase and incident hypertension; in contrast, in Hispanic Americans[11], GRS was constructed by 2 SNPs on chromosome 3 alone, and when GRS was added into the model, the improvement of predicting capability measured by the AUC was minor. In a Korean population[26], GRS was constructed by 4 SNPs based on GWAS, which was independently associated with the risk of incident hypertension. Among the 4 SNPs, rs17249754 was the same predictor as that selected in 2 Chinese genetic studies [19,21], and rs1378942 was the same as that used in the Swedish genetic study[14]. However, adding GRS into models with traditional risk factors did not significantly improve the discrimination ability. In the Swedish study[14], when adding cGRS (derived from a simple, unweighted count method) into the traditional model, AUC was marginally, but not significantly, improved (from 0.662 to 0.664). In the 29 SNPs that constructed cGRS, one (rs1378942) was the same as that selected in Korean study[26] and two (rs16998073,
rs11191548) were the same as those selected in 2 Chinese studies[19,21]. A couple of factors may contribute to these unfavorable observations. First, since hypertension is a known multi-gene disease, a limited number of SNPs as representative predictors may not fully reflect the overall contribution and weight of all genetic variants. Second, it is possible that some of those included SNPs were selected without fully considering their potential interactions with other genetic variants or environmental factors.

In contrast, in a Chinese study[21], adding GRS constructed by 22 carefully selected SNPs to the traditional predictors produced an ideal result, as the C-index value improved significantly (C-index change = 0.3%–0.5%; all \( p < 0.05 \)). Among the 22 uncorrelated \( (r^2 < 0.5) \) SNPs, 10 were associated with SBP or DBP from published GWAS data obtained from an East Asian population, and 19 SNPs had been identified and verified in a Chinese population. These results clearly suggested that the contribution and value of GRS to a hypertension prediction model heavily depends on the selection of SNPs. Since hypertension is a disease of polygenic inheritance, the selection of SNPs used for GRS construction is thus critical. Using GWAS results as the only source for SNP selection is inadequate, as the characteristics of SNPs obtained from one particular GWAS may not necessarily be suitable for other ethnic populations. More appropriate SNP selection should come from the genetic research results in the same ethnic group. Other SNP selection considerations for GRS construction should include a sufficient number of SNPs, causal relationship between the select genes and disease development, gene-gene or gene-environment interactions, and proper statistical methods to include or exclude gene loci.

At the present stage, genetic markers for predicting hypertension can be of great interest for researchers and basic scientists (and possibly for drug companies), but may not hold much interest for patients. Once genetic factors are included in prediction models, patients cannot use the model for self-assessment, clinicians could face problems explaining the model, and cost for genetic tests can be high. These problems may be resolved with the development of gene-function and gene-sequencing research.

Model validation

Seven studies validated their prediction models using internal validation. All studies indicated good discriminatory ability and calibration, suggesting that the models could be applied in the original population with satisfactory performance. A Framingham prediction model was validated in external populations by 7 studies (S3 Table). It performed well in a study of African-American and Caucasians in the US[35], a German study[15] and a British study[12]. In a large nationwide Korean cohort,[33]the AUC was acceptable, but this model underestimated hypertension incidence \( (p<0.001) \) in Korea. In the Multi-Ethnic Study of Atherosclerosis (MESA)[34], including Caucasian, African-American, Hispanic, and Asian (primarily of Chinese descent) participants, the Framingham model showed better discrimination ability than SBP alone or age-specific DBP categories. However, the difference between the observed and the predicted hypertension risks (Hosmer-Lemeshow goodness of fit \( p<0.001 \)) in the MESA study was significant. In contrast, the discrimination \( (C\text{-statistics } = 0.5 \text{ to } 0.6) \) and calibration ability \( (p<0.0001) \) in rural Chinese was poor[36], whereas poor agreement \( (\chi^2 = 29.73, p = 0.0002) \) underestimated the risk of hypertension in Koreans[24]. The distinct performance in different populations was partially attributed to the various levels of risk predictors and inherited variables. These differences suggested that a model derived from one particular population could not be directly applied to a distinct population, and the fittest model for one particular population is that derived from the same population.
Heterogeneity

The meta-analysis showed the heterogeneity was significant. The included variables, study designs, number of participants, populations, statistical methods, and follow-up times were different from each other, which might be the source of heterogeneity. We attribute this to the specialization of prediction models, which need to be built for various populations, because no one model could be applied to all people.

Clinical implications

Currently, a large issue regarding hypertension prediction models/scores is that nobody uses these scores in daily life or clinical practice beyond research publications. Some people even question whether hypertension needs to be predicted, as it can be easily measured with non-invasive, cheap, and accessible methods. The function of these models is not only to predict the occurrence of hypertension but, more meaningfully, to remind patients and physicians to pay attention to BP. What is more, it has been proved that the process of progression from normotensive or prehypertension to hypertension can be delayed or prevented by proper and timely clinical interventions. It is urgent and meaningful for people to conduct timely interventions. The importance of prediction models/scores needs to be widely disseminated by authorities or the media to promote their application.

Strengths and limitations of existing models

Most of the current predictors are data commonly collected in routine clinical practice, which are relatively easier for both health-care providers and patients to access. Some models are in the form of risk scores, which may still have room to improve but are also convenient to use in routine clinical practice. Furthermore, several models took GRS into account, which could contribute significantly to their prediction accuracy of hypertension. Since the performance of all these prediction models was accepted as good, the application of these models in clinical practice is very promising.

In contrast, several limitations of these prediction models are also noted. First, since not all these studies were specifically designed or conducted for generating prediction models, the clinical data collection may not be complete, and quality of data collected to inform these models also varies greatly; thus, prediction accuracy is a concern. Second, the enrollment number of participants was low in some studies and may not represent the true characteristics of the general population. Third, the various levels of risk predictors and inherited variables between populations made the models inapplicable for other general people. Fourth, a justified method in selecting the suitable SNPs is lacking. Fifth, since most of the BP data were obtained in hospital or clinic settings, the “white coat effect” may influence the outcome of the BP measurement. Sixthly, none of these models have been shown to improve outcomes in prospective research. Lastly, only a few models were indeed validated by internal cohorts, and only 3 were validated in external cohorts. The validation in internal cohort is more or less considered as a repeat of the original cohort and thus may be overoptimistic in its prediction performance results.

Conclusion

Recently, more and more hypertension prediction models have been reported in different countries and among various ethnic populations. Most of the reported predictors are commonly used in routine clinical practice, and the role of genetic factors is earning more attention. However, the incorporation of genetic variation does not improve the performance
significantly for all models. The selection of gene loci is critical, and a justified method in selecting the suitable SNPs is needed. The current reported models have satisfying discrimination and calibration ability, but the validation of these models is still insufficient, which is a critical and required step prior to their broad application in daily clinical practice.

**Perspective of future research**

It is obvious that the current prediction models might not be perfect, but they do provide a solid foundation for future studies. Of course, more studies on prediction models of hypertension should be conducted with large enrollment numbers, complete data collection, experienced or well-trained investigators, and appropriate statistical analysis. With the development of genetic research, more hypertension-associated SNPs will be found, and a standard protocol in gene loci selection as a candidate prediction factor will be needed. Indeed, before any models are used as guidelines, they need to be validated in various cohorts and adjusted accordingly.

**Supporting information**

S1 Fig. Begg’s and Egger’s publication bias plot. (TIF)

S1 Table. PRISMA 2009 checklist. (DOC)

S2 Table. SNPs of GRS. SNP: single nucleotide polymorphism; GWAS: Genome Wide Association Study; NR: not reported. Rs1378942 was chosen in both Sweden and Korean studies; rs17249754 in Korean and 2 Chinese studies; rs11191548 and rs16998073 from Sweden were the same in two Chinese studies; in two Chinese studies, 7 SNPs (rs17030613, rs16849225, rs1173766, rs11066280, rs35444, rs880315 and rs17249754) were the same. (DOCX)

S3 Table. External validation of the Framingham model. AUC means the area under the receiver operating characteristic curve; CI means confidence interval; JNC—VII definition means the definition of hypertension is based on the Joint National Committee (JNC)—VII definition of hypertension (i.e., SBP/DBP ≥140/90 mmHg or use of antihypertension medications); NR means not reported. First author and year represent study. (DOCX)

S1 File. Results of meta-analysis and publication bias test. (DOCX)

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