Sex differences in chronic kidney disease prevalence in Asia:  

a systematic review and meta-analysis

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ABSTRACT

Background

Previous reports on the prevalence of chronic kidney disease (CKD) in Asia have suggested important sex disparities but have been inconsistent in nature. We sought to synthesise available sex-disaggregated CKD prevalence data in Asia to quantify sex disparities in the region.

Methods

We systematically searched MEDLINE and EMBASE for observational studies involving ≥500 adults that reported sex-disaggregated CKD prevalence data in any of the 26 countries in East, Southeast, or South Asia. For each study, we calculated the female: male prevalence ratio (PR), with a ratio >1 indicating a higher female prevalence. For each country, log-transformed PRs were pooled using random effects meta-analysis.
These were then combined using a fixed effect model, weighting by population size, to estimate a pooled PR for each of East, Southeast, and South Asia, and Asia overall.

Results

Sex-disaggregated data were available from 171 cohorts, spanning 15 countries, and comprising 2,550,169 females and 2,595,299 males. Most studies (75.4%) came from East Asia (China, Taiwan, Japan, and South Korea). Across Asia, CKD prevalence was higher in females (pooled prevalence 13.0% [95% CI 11.3-14.9%]) compared with males (pooled prevalence 12.1% [10.3-14.1%]), with a pooled PR of 1.07 (0.99-1.17). Substantial heterogeneity was observed between countries. The pooled PRs for East, Southeast, and South Asia were 1.11 (1.02-1.21), 1.09 (0.88-1.36), and 1.03 (0.87-1.22), respectively.

Conclusions

Current evidence suggests considerable between-country and -region heterogeneity in the female: male PR of CKD. However, there remains a large part of the region where data on sex-specific CKD prevalence are absent or limited. Country-level assessment of the differential burden of CKD in females and males is needed to define locally relevant policies that address the needs of both sexes.

Keywords: albuminuria, CKD, epidemiology, gender, systematic review
**INTRODUCTION**

Chronic kidney disease (CKD) is a major cause of morbidity and mortality worldwide. In 2017, it was estimated that almost 700 million individuals worldwide were living with CKD, with 1.2 million deaths and 35.8 million disability-adjusted life-years (DALYs) directly attributed to the disease.\(^1\) Generally defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73\(^2\) and/or a urine albumin-to-creatinine ratio (UACR) ≥30 mg/g (≥3 mg/mmol),\(^2\) CKD is associated with a wide range of adverse health outcomes. The most prominent include an increased risk of cardiovascular disease (CVD) and hypertension, but mineral and bone disorder, anaemia, and infection are also common in patients nearing kidney failure.\(^3\) Moreover, adverse effects of CKD on health-related quality of life, including for milder CKD stages, have been reported.\(^4\)–\(^7\)

Similar to other major chronic diseases (e.g. diabetes and coronary heart disease), there is accumulating evidence that females and males are differentially affected by CKD, in terms of prevalence, disease progression and health outcomes.\(^8\)–\(^9\) However, research in this area remains limited and there is uncertainty around the magnitude and direction of these differences, which themselves likely vary by outcome and geographically. In Asia, the unique aetiological profile of CKD,\(^10\)–\(^12\) together with the ongoing epidemiological transition\(^13\)–\(^14\) and vast sociocultural diversity, make generalisations of sex- and gender-based findings from other parts of the world particularly challenging. Understanding regionally specific sex differences in CKD burden will be important to inform health policy and planning and guide future research.

The aim of this systematic review and meta-analysis is to provide a comprehensive assessment of sex differences in CKD prevalence in Asia, the region projected to experience the greatest increase in disease burden.
MATERIALS AND METHODS

Search strategy and selection criteria

This systematic review and meta-analysis was performed in accordance with Meta-Analyses Of Observational Studies in Epidemiology (MOOSE) guidelines.\textsuperscript{15}

We identified relevant studies by searching MEDLINE (from 1946 to January 23, 2020) and EMBASE (from 1980 to January 23, 2020), using broad keywords and Medical Subject Headings (MeSH) related to kidney function, proteinuria and Asian countries (S1 Search Strategy). The same search was repeated on May 24, 2021 to identify papers published since January 2020, ensuring that the final review was as comprehensive and up-to-date as possible. The persons conducting the search were CH and MJu, both of whom are PhD-level trained epidemiologists. In addition, reference lists of all included studies were manually searched to identify additional studies not captured in the online search. Authors of relevant studies were contact via email if further information was required.

Observational studies involving \( \geq 500 \) adults (aged 18 years and older), conducted in East, Southeast, or South Asia, that reported sex-disaggregated CKD prevalence data were included. Single-sex studies were excluded.\textsuperscript{16} We included studies in which the primary objective was to assess CKD prevalence, or CKD prevalence was reported as part of the baseline participant characteristics. If there was overlap in the cohort used across multiple studies, the one with the broadest inclusion criteria or largest sample size was used. We excluded reviews, letters to the editor, case reports, and case series, and restricted our review to studies published in English but placed no restriction on language in the literature search. CKD was defined as eGFR >60 mL/min/1.73m\(^2\) with albuminuria (urine albumin-to-creatinine ratio [UACR] >30 mg/g \([>3 \text{ mg/mmol}]) or proteinuria (as defined by the authors),\textsuperscript{2} or eGFR <60 mL/min/1.73m\(^2\).
Data extraction and quality assessment

Abstract review, data abstraction, and risk of bias assessment were performed independently by two reviewers (LB and AT). Any disagreements were adjudicated by a third reviewer (CH and MJ). Data from the included studies were extracted using a standardised data extraction spreadsheet. Extracted information included study design, setting, source population and selection criteria, number of females and number of men, mean age, percentage of people with diabetes, percentage of people with hypertension, definition of CKD (based on eGFR and albuminuria/proteinuria, eGFR only and albuminuria/proteinuria only), eGFR equation used, and sex-specific CKD prevalence.

Risk of bias was assessed using a modified version of the Newcastle-Ottawa Quality Assessment Scale for cohort studies. Each study was assessed against five items: (i) representativeness of the sample, (ii) sample size (<4000 and ≥4000 participants), (iii) comparison of patient characteristics between the CKD cohort and the non-CKD cohort, (iv) outcome ascertainment, and (v) reporting of descriptive statistics (mean and standard deviation or median and interquartile interval for continuous variables, and counts and percentages for categorical variables). For each item on the scale, the study received a score of 0, denoting either insufficient information or evidence that the study did not meet the criteria requirement, or 1, denoting sufficient information to indicate a low risk of bias. The scores were then summed to obtain a final risk score. Studies with a score of 1–2, 3 and 4–5 were classified as having a high, medium, and low risk of bias, respectively.

Data analysis

Primary analysis

For each study, sex-specific prevalence was calculated as the percentage of females or males identified as having CKD. The prevalence in females was divided by the prevalence in males to obtain the female:male prevalence ratio (PR), with a PR >1 indicating a higher prevalence in females. Prevalence estimates and the corresponding PRs were log-transformed prior to pooling. For each country, DerSimonian-Laird random
effects models were used to estimate the pooled sex-specific CKD prevalence estimates and the pooled PR.\textsuperscript{19} These country-stratified pooled estimates were then further meta-analysed using fixed effect models, with weighting by country population size, to derive pooled estimates for East Asia, Southeast Asia, South Asia, and Asia overall. Population estimates for 2019 were obtained from the United Nations Population Division (https://population.un.org/wpp/DataQuery/, accessed 22 October 2020).

Subgroup analyses

To examine possible causes of heterogeneity (irrespective of country), subgroup analyses were done by sample size (N<4000 and N\text\geq4000), percentage of females in the study cohort (<median of 52.1% and \text\geqmedian), mean age of study cohort (<65 years and \text\geq65 years), percentage of individuals with diabetes (<median of 31.2% and \text\geqmedian), percentage of individuals with hypertension (<median of 61.8% and \text\geqmedian), eGFR equation (CKD-EPI,\textsuperscript{20} MDRD,\textsuperscript{21} and other) and risk of bias (low, medium, and high). The Cochran’s Q-statistic for the null hypothesis of homogeneity was used to assess heterogeneity between the subgroups.

Sensitivity analyses

We performed a series of sensitivity analyses to test the robustness of our findings. First, we removed studies that had a strong influence on the country-level pooled PR estimates. These were identified using a combination of studentised residuals (with an absolute threshold of 2 indicating an outlier), leave-one-out analyses and diagnostic plots of the Cook’s distance.\textsuperscript{22} Second, meta-analyses were repeated using only high-risk cohorts, defined as participants selected based on the presence of diabetes, hypertension, any CVD, or aged \text\geq65 years, and using cohorts sampled from non-high-risk populations (e.g. general population or hospital populations attending an annual health check). Previous work has shown that diabetes, hypertension and CVD might progress differently in females compared to males.\textsuperscript{23-26} Given that these conditions are strongly associated with CKD, it is possible that their differential effects in females and males are reflected in sex differences in CKD prevalence that are specific to multimorbidity. Analyses were also
repeated using the largest study from each country.\textsuperscript{27} We also performed sensitivity analyses for different definitions of CKD, in which we included studies that assessed CKD based on both eGFR and albuminuria/proteinuria, on eGFR alone, and on albuminuria/proteinuria alone. For studies that assessed and reported on both measurements, we extracted prevalence data for each of the measures separately. Finally, analyses were repeated for advanced CKD (KDIGO Stages 4–5), but were restricted to studies with at least 10 occurrences of advanced CKD events in each of the sexes.

Meta-analyses were performed in R 4.1.0 using the \textit{metafor} package (v 3.0-2),\textsuperscript{19} with forestplots generated using the \textit{forestplot} package (v 1.10-1)\textsuperscript{28} and maps using the \textit{sf} (v 1.0-4)\textsuperscript{29} and \textit{tmap} (v 3.3-2)\textsuperscript{30} packages.

\section*{RESULTS}

\textit{Search results and characteristics of included studies}

Our initial database search identified 7,200 studies in January 2020 and a further 4,411 in May 2021 (total 11,611), of which 995 articles qualified for full-text review. A further 132 studies were identified through manual searches. In total, 168 studies met the inclusion criteria during full-text review, of which one reported data from three countries and one from two countries (Figure 1).

Sex-disaggregated CKD prevalence data were available for 15 of the 26 Asian countries, involving 2,550,169 females and 2,595,299 males. Most of the studies (75.4\%) and participants (91.2\% of females and 89.7\% of males) came from East Asia (China, Taiwan, Japan, or South Korea) (Table 1). Thirty-eight per cent (n=65) were conducted in high-risk cohorts and 62.0\% (n=106) involved non-high-risk cohorts. Around a quarter (n=43) of studies defined CKD based on \textit{either} a reduced eGFR (<60 mL/min/1.73\textsuperscript{2}) or the presence of albuminuria or proteinuria, 62.5\% (n=113) studies defined CKD based on a reduced eGFR alone, and 11.1\% (n=15) based only on the presence of albuminuria or proteinuria. Of the 156 studies that measured eGFR to ascertain CKD status, 51.3\% (n=80) used the MDRD equation, 25.0\% (n=39) used the CKD-EPI equation, 12.8\%
(n=20) used a different equation, and 8.3% (n=13) did not specify the equation used. The characteristics of individual studies are provided in S1 Table.

The risk of bias assessment indicated that 89 (52.0%) studies had a low risk of bias (score of 4–5), 61 (35.7%) had a medium risk of bias (score of 3) and 21 (12.3%) had a high risk of bias (score of 1–2).

**Sex disparities in CKD prevalence**

Reported sex-specific CKD prevalence estimates varied substantially between the studies (S1 Table). Across Asia, the pooled prevalence of CKD based on all included studies was 13.0% (95% CI 11.3–14.9%) in females and 12.1% (95% CI 10.3–14.1%) in males (Figure 2 and Supplementary Figure 1). The pooled prevalence of CKD was higher in females compared with males (PR 1.07 95% CI 0.99–1.17). There was substantial between-country heterogeneity ($I^2 = 87.4$%), with the PR ranging from 0.75 (95% CI 0.53–1.08, n=1) in Indonesia to 2.73 (95% CI 1.81–4.12, n=1) in Vietnam. China and India, the two largest countries in Asia, had a pooled PR of 1.11 (95% CI 1.02–1.21, n=46) and 0.91 (95% CI 0.75–1.11, n=11), respectively. The strongest evidence for a higher CKD prevalence in females came from East Asia, with a pooled PR of 1.11 (95% CI 1.02–1.21), driven by the large population size of China. In contrast, there was no evidence for a sex difference in either Southeast Asia (PR 1.09 [95% CI 0.88–1.36]) or South Asia (PR 0.98 [95% CI 0.85–1.22]).

**Subgroup and sensitivity analyses**

In subgroup analyses of all studies (i.e. not stratifying by country), no differences in the pooled PRs were observed for the subgroups examined, including the different risk of bias categories (Supplementary Figure 2). Overall, results were largely consistent in sensitivity analyses in which influential outliers were removed from the country-level meta-analysis (pooled PR for Asia: 1.06 [95% CI 0.99–1.14]; Supplementary Figure 3), as well as those in which studies were restricted to either non-high-risk or high-risk population cohorts [pooled PRs for Asia: 1.06 [95% CI 0.96–1.17] and 1.04 [95% CI 0.96–1.13], respectively; Supplementary
There were notable differences in the pooled PR for Asia when only the largest study from each country was used (pooled PR: 1.16 (95% CI 1.10–1.22). At the country and sub-regional levels, the robustness of our findings to the specific study inclusion criteria (i.e. non-high-risk or high-risk cohorts) varied between countries or sub-regions. Estimates were particularly variable in countries and regions where the evidence base was limited.

In analyses involving studies in which CKD was defined according to both eGFR and albuminuria/proteinuria (n=43; 11 countries), the pooled PR was 0.91 (95% CI 0.81-1.03). The pooled PR for reduced kidney function (eGFR <60 mL/min/1.73²) was 1.21 (95% CI 1.03-1.44, n=140 from 15 countries), whilst for albuminuria/proteinuria, it was 0.94 (95% CI 0.82-1.07, n=39 from 10 countries) (Supplementary Figures 8-13).

When restricted to the 9 countries where sex-disaggregated prevalence data for advanced CKD (KDIGO stages 4-5) were available, the pooled PR for advanced CKD for Asia was 1.04 (95% CI 0.72–1.48; Supplementary Figure 14). Once again, heterogeneity between countries was observed ($I^2 = 81.7\%$). The pooled PRs for East Asia, Southeast Asia, and South Asia were 1.17 (95% CI 0.82–1.66), 1.03 (95% CI 0.67–1.60) and 0.89 (95% CI 0.45–1.78), respectively.

**DISCUSSION**

In a pooled analysis of 171 cohorts, comprising 2,550,169 females and 2,595,299 males from 15 Asian countries, the overall prevalence of CKD in the region was 1.07 (95% CI 0.99–1.17) times higher in females compared with males, but with considerable variation between countries. Of note, China and India, which account for 61% of the Asian population, showed contrasting sex differences; in China, the prevalence of CKD was higher in females, whilst, in India, a similar prevalence between the sexes was observed. Collectively, these findings highlight the need for (i) more widespread sex-disaggregated data collection and
CKD burden estimation in Asia, and (ii) targeted CKD detection and management approaches that consider the local differences in the sex-specific burden of CKD.

Our finding that the prevalence of CKD is overall higher in females compared to males is consistent with previous systematic reviews.\textsuperscript{27,31,32} In 2016, a meta-analysis of 51 studies reporting sex-specific CKD prevalence found a mean prevalence of CKD of 14.6% in females and 12.8% in males, corresponding to a female:male PR of 1.14.\textsuperscript{31} More recently, the 2017 Global Burden of Disease (GBD) Study reported that the global age-standardised prevalence of CKD was 1.29 (95% uncertainty interval [UI] 1.28–1.30) times higher in females than in males.\textsuperscript{33} However, the global scope of these analyses comes at the cost of granularity, potentially masking any geographic variation in the observed sex differences. The only study to examine sex-specific CKD prevalence at a country level did not report any measures of uncertainty in the observed differences.\textsuperscript{32} Our review addresses these two important limitations and provides the most comprehensive, up-to-date review of sex differences in CKD prevalence across Asia.

It is generally purported that, for any given age, the prevalence of milder forms of CKD (KDIGO stages 1-3) is higher in females, whilst the opposite is true for kidney failure (KDIGO stage 5).\textsuperscript{8,27,32,34} However, existing studies are limited by their reliance on kidney replacement therapy registry data, which in part reflects system-level access to care or personal preferences around care, rather than the burden of the disease itself.\textsuperscript{35} In the present study, which predominantly included studies that actively measured kidney function, the prevalence of CKD stages 4-5 for Asia was similar between the sexes (pooled PR 1.04 [95% CI 0.72-1.48]). Given that this is based on data from only 27 studies across the region, it is possible that we had insufficient power to detect a difference in prevalence between the sexes. It is interesting, however, that, in all countries where data were available, the pooled female:male PR indicated either no sex difference or a higher female prevalence. Countries where there was evidence of a higher female prevalence of advanced CKD were Japan (PR 1.24 [1.07-1.45], n=7), Singapore (PR 1.16 [1.05-1.27], n=1), Bangladesh (PR 1.48 [1.45-1.52], n=1) and Iran (PR 1.97 [1.09-3.56], n=1). Where the female-specific prevalence of
advanced stages of CKD is higher, this may be explained by differential survival rates between females and males; at each level of kidney function, the CKD mortality rate has been shown to be higher in men. However, gendered factors, such as adherence to guideline-recommended medications, receipt of evidence-based care, and social norms around access to care, may also play a role. Nevertheless, it raises important questions around the need for gender-sensitive CKD research and health planning in the region.

For instance, the extent to which women are disproportionately burdened by CKD may be particularly heightened in countries with high out-of-pocket medical costs, compounded by lower lifetime earnings and longer life expectancy in women relative to men. It is also important to consider that women with CKD have a higher risk of pre-term delivery and intrauterine growth restriction (IUGR), resulting in infants being born with a low birth weight and/or who are small for their gestational age. This has implications for the burden of CKD and other non-communicable diseases in future generations, with evidence that both low birth weight and being small for gestational age increases the long-term risk of kidney failure, hypertension and diabetes. Increasing awareness of CKD among women of child-bearing age and early detection of CKD should therefore be a priority. For women already living with CKD, efforts are needed to improve treatment rates and outcomes, which have been previously shown to be sub-optimal among women compared to men. Furthermore, a better understanding of the sex-specific mortality rate associated with CKD in Asian populations is needed to ensure that the needs of both women and men are appropriately addressed. Across the region, sex-disaggregated data collection, analysis and reporting should be embedded into CKD monitoring and surveillance systems as they are being developed.

Reasons for the observed sex differences are likely manifold. Several recent reviews on the role of sex and gender in CKD have highlighted a complex interplay of biological, behavioural, cultural and socioeconomic factors that may contribute to observed disparities. While the data used in this study cannot shed light on why sex differences may occur, we can speculate that the observed differences are the result of interactions between diverse factors, including both gendered factors related to health-related behaviours.
and access to care, and biological factors influencing progression of disease and the underlying pathophysiological processes involved. For instance, whilst not statistically significant, the suggestion of a higher female:male PR in studies with a higher percentage of participants with diabetes or hypertension provides support for the hypothesis that the effect of these conditions on the risk of CKD might vary between the sexes, as has been observed for a range of vascular diseases. Among women, pregnancy-induced hypertension or gestational diabetes leading to a higher risk of hypertension and CVD post-pregnancy, and in turn CKD, may also play a role. Local investigations into the reasons underpinning the sex differences are needed.

We observed significant between-country heterogeneity in the pooled female:male PRs, which may be attributable to several factors. First, the availability of data varied across the region and we found that pooled estimates for countries with limited data (e.g. Singapore) were generally less robust against the types of cohorts (high-risk, non-high-risk, or both) used in the meta-analysis. In contrast, for pooled analyses where a large number of studies were available (e.g. Asia overall or in China), decisions around which types of cohorts to include did not markedly effect the pooled PR. It is possible, therefore, that the absence of a sex difference in some countries or sub-regions is simply the result of there being insufficient data to detect a difference.

Second, formulae used to estimate GFR varied between studies, the most common one being the MDRD equation (n=80; 51.3% of studies that measured eGFR). Whilst the MDRD equation can yield higher prevalence estimates compared to the CKD-EPI equation (the current gold-standard), our subgroup analysis of studies using different eGFR equations showed no difference in the pooled PRs. However, it remains possible that differences in the performance of eGFR formulae in different country settings may have contributed to the observed between-country heterogeneity. Validation studies conducted in community-based populations with appropriate age and ethnic diversity are needed to assess the impact of different GFR estimation methods on sex-specific CKD prevalence in this region.
Third, both the MDRD and CKD-EPI equations include sex as a variable, and assume that, for a given serum creatinine level, kidney function will be lower in females compared to males. This has led some to argue that the ascertainment of CKD based on these equations may overestimate CKD prevalence in females compared to males, particularly in the intermediate stages. Indeed, this might in part explain the higher female: male PR that was observed for studies that reported on the prevalence of a reduced eGFR in our sensitivity analyses (PR 1.21 [1.03-1.44] compared to PR 0.94 [0.82-1.07] in studies that only assessed urine protein), and could account for some of the heterogeneity in results between countries. For example, in Thailand, where the pooled PR was 1.14 (95% CI 1.04-1.26), three of the four included studies defined CKD based only on eGFR and the fourth assessed albuminuria as well. In comparison, only 2 of the 11 studies from India defined CKD using only eGFR, 8 assessed both measures and 1 assessed only albuminuria; the pooled PR estimate was 0.91 (95% CI 0.75-1.11). However, it is worth noting that between-country heterogeneity remained high even in analyses that only included the prevalence of a reduced eGFR (I² = 90.0%) and that considerably fewer studies defined CKD using only albuminuria/proteinuria assessments (n=39).

Limitations of our meta-analysis are inherent to the use of published data. Data were limited, or even absent, for a large part of the region, with only 42 studies available outside of East Asia. No data on sex-specific CKD prevalence were available for 11 countries: Afghanistan, Bhutan, Brunei, Cambodia, Democratic People’s Republic of Korea, Laos, Maldives, Mongolia, Myanmar, the Philippines and Timor-Leste. There was also extensive heterogeneity between studies, in terms of their sampling methodology and eligibility criteria, definition of CKD, assays used and study period. Nevertheless, most studies were found to have a low or medium risk of bias. In addition, few studies fully staged CKD based on both eGFR and albuminuria categories, as recommended by KDIGO CKD guidelines, precluding the assessment of sex differences in each of the separate stages. Finally, the exclusion of articles published in languages other than English may have led to some important studies being missed.
In conclusion, our findings highlight the need for ongoing country-level assessment of sex differences in CKD prevalence such that locally relevant policies can be developed that address the needs of both females and males. As global capacity for CKD surveillance is strengthened over the next 5-10 years, it will be important for sex- and gender-disaggregated data collection and reporting to be embedded within monitoring programmes as they are being developed.

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DATA AVAILABILITY STATEMENT

Most of the data underlying this article are available in the article and in its online supplementary material. Data not included in the article (e.g. studies that were excluded from analyses) will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

CH, LB, AT, AB and TT have no conflicts of interest to declare.

SB has served on the advisory board of AstraZeneca, Bayer and Vifor Pharma; has received speaker’s honoraria from Bayer, Pfizer and Vifor Pharma; and has received in-kind research support from Bayer. All fees have been paid to his institution.

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Committees for trials sponsored by Chinook, CSL Behring and Janssen; serves on a Steering Committee for an investigator-initiated trial with funding support from Dimerix; and has spoken at scientific meetings sponsored by Amgen, Janssen, Roche and Vifor Pharma. Any consultancy, honoraria or travel support has been paid to her institution.

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Figure 1 Flow diagram of study selection.

*One article reported data from three countries and one reported data from two countries.
Figure 2 Sex-specific CKD prevalence estimates and female: male prevalence ratio (PR), pooled by country (estimated using random effects meta-analysis) and by region (estimated using fixed effect meta-analysis of country-stratified pooled estimates). For the fixed effect meta-analysis, country-level estimates were weighted by country population size.
| Country     | No. of studies (high-risk; non-high-risk) | Total no. of participants (% female) | Median no. of females (IQI) | Median no. of males (IQI) | Median % of people with diabetes (IQI) | Median % of people with hypertension (IQI) | Interval of reported mean age |
|-------------|----------------------------------------|-------------------------------------|-----------------------------|---------------------------|---------------------------------------|------------------------------------------|-----------------------------|
| Asia        | 171 (65;106)*                          | 5,139,384 (49.6)                   | 1,866 (636-6,012)          | 1,913 (655-5,076)           | 17.0 (8.6-36.6)                         | 40.4 (26.5-57.8)                         | 35.6-102.8†                 |
| East Asia   | 129 (54; 75)                           | 4,648,661 (50.0)                   | 2,123 (647-7,141)         | 2,178 (794-7,791)           | 15.3 (8.4-36.1)                         | 43.8 (27.4-58.3)                         | 36.0-102.8†                 |
| China       | 46 (18; 28)                            | 788,307 (45.2)                     | 1,865 (780-6,144)         | 1,990 (739-5,136)           | 18.4 (9.6-38.6)                         | 48.9 (33.0-63.4)                         | 41.8-102.8                  |
| Taiwan      | 21 (9; 12)                             | 799,479 (50.0)                     | 3,075 (647-13,699)        | 3,393 (1,142-12,991)       | 19.5 (8.8-36.9)                         | 38.6 (23.3-59.8)                         | 36.0-74.9                   |
| South Korea | 18 (7; 11)                             | 1,139,257 (40.8)                   | 5,189 (858-16,741)       | 4,353 (1,882-13,441)       | 19.1 (9.3-31.5)                         | 30.0 (21.8-48.8)                         | 41.7-76.0                   |
| Japan       | 44 (20; 24)                            | 1,921,618 (57.6)                   | 1,891 (404-6,176)        | 1,686 (620-4,132)           | 13.9 (5.4-34.4)                         | 45.1 (29.9-55.1)                         | 40.0-74.2                   |
| Southeast Asia | 12 (5; 7)                        | 127,529 (51.9)                     | 1,278 (755-2,589)       | 1,446 (471-3,225)           | 39.0 (17.7-85.7)                       | 55.0 (35.6-59.9)                         | 48.8-65.9                   |
| Indonesia   | 1 (0; 1)                               | 1,496 (63.4)                       | 949                       | 547                        | Not reported                           | Not reported                            | Not reported                |
| Malaysia    | 3 (2; 1)                               | 8,519 (22.5)                       | 595 (560-697)             | 471 (419-618)               | 40.3 (30.0-70.2)                       | 55.8 (53.4-58.3)                         | 48.8-55.4                   |
| Singapore   | 3 (1; 2)                               | 95,609 (52.1)                      | 1,606 (1,238-24,469)     | 3,923 (2,184-22,679)       | 37.6 (27.3-40.2)                       | 56.6 (55.0-69.9)                         | 62.9-65.9                   |
| Thailand    | 4 (2; 2)                               | 13,400 (59.9)                      | 2,158 (1,574-2,589)      | 1,446 (1,110-1,681)        | 56.3 (12.4-100.0)                      | 42.5 (27.1-63.4)                         | 61.4-61.6                   |
| Vietnam     | 1 (0; 1)                               | 8,505 (64.8)                       | 5,513                     | 2,992                      | Not reported                           | Not reported                            | 30.5                       |
| South Asia  | 30 (6; 24)                             | 363,194 (43.4)                     | 1,055 (625-2,430)        | 1,243 (557-3,136)           | 14.0 (7.5-21.6)                        | 31.2 (16.7-41.6)                         | 35.6-67.5                   |
| Bangladesh  | 4 (3; 1)                               | 222,591 (43.6)                     | 728 (586-2,377)          | 690 (573-31,529)            | 61.2 (41.8-80.6)                       | 58.4 (37.5-79.2)                         | 47.0-56.7                   |
| India       | 11 (1; 10)                             | 37,549 (48.6)                      | 1,154 (942-1,982)        | 1,112 (849-2,662)           | 8.6 (6.1-17.6)                         | 31.2 (16.7-33.6)                         | 35.6-51.0                   |
| Nepal       | 1 (0; 1)                               | 20,811 (61.5)                      | 12,792                   | 8,019                      | Not reported                           | Not reported                            | 39.0                       |
| Pakistan    | 3 (1; 2)                               | 5,183 (52.3)                       | 796 (606-1,148)          | 1,374 (822-1,499)           | 19.0 (18.6-20.2)                       | 72.1 (58.1-86.0)                         | 51.5-56.7                   |
| Sri Lanka   | 2 (1; 1)                               | 6,949 (54.8)                       | 1,904 (1,224-2,584)      | 1,571 (911-2,230)           | 20.6 (11.8-29.3)                       | 52.6 (28.8-76.3)                         | 62.9                       |
| Country | N (95% CI) | Mean Age (95% CI) | Median Age (90% CI) |
|---------|------------|--------------------|--------------------|
| Iran    | 9 (0; 9)   | 70,111 (32.8)      | 760 (503-5,840)    |
|         | 1,399 (481-4,223) | 13.7 (9.4-14.0) | 25.8 (17.2-38.0) |
|         | 39.8-67.5  |

*In total, 168 studies met our inclusion criteria, with one of these reporting data from three countries and one from two countries. The total number of data points is therefore 171.

†The highest mean age of 102.8 years is from a study that specifically recruited individuals aged 100 years and older.