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Irawati, Sylvi; Wasir, Riswandy; Floriaan Schmidt, Amand; Islam, Atiqul; Feenstra, Talitha; Buskens, Erik; Wilffert, Bob; Hak, Eelko

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REVIEW

Long-term incidence and risk factors of cardiovascular events in Asian populations: systematic review and meta-analysis of population-based cohort studies

Sylvi Irawati^{a,b}, Riswandy Wasir^{c,d}, Amand Floriaan Schmidt^{a,e,f}, Atiqul Islam^{a,g}, Talitha Feenstra^c, Erik Buskens^c, Bob Wilffert^a and Eelko Hak^a

^aGroningen Research Institute of Pharmacy, PharmacoTherapy, Epidemiology & Economics, University of Groningen, Groningen, the Netherlands; ^bCenter for Medicines Information and Pharmaceutical Care, Faculty of Pharmacy, Universitas Surabaya, Surabaya, Indonesia; ^cFaculty of Medical Sciences, Epidemiology, University Medical Center Groningen, Groningen, the Netherlands; ^dSekolah Tinggi Ilmu Farmasi, Makassar, Indonesia; ^eUniversity College London, Institute of Cardiovascular Science, London, UK; ^fDepartment of Cardiology, Division Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands; ^gDepartment of Statistics, Shahjalal University of Science and Technology, Sylhet, Bangladesh

ABSTRACT

Background: Scientific studies on cardiovascular disease (CVD) burden and risk factors are predominantly based on short-term risk in Westerner populations, and such information may not be applicable to Asian populations, especially over the longer term. This review aims to estimate the long-term (>10 years) CVD burden, including coronary heart disease (CHD) and stroke, as well as associated risk factors in Asian populations.

Methods: PubMed, Embase and Web of Science were systematically searched, and hits screened on: Asian adults, free of CVD at baseline; cohort study design (follow-up >10 years). Primary outcomes were fatal and non-fatal CVD events. Pooled estimates and between-study heterogeneity were calculated using random effects models, *Q* and *I*² statistics.

Results: Overall, 32 studies were eligible for inclusion (follow-up: 11–29 years). The average long-term rate of fatal CVD is 3.68 per 1000 person-years (95% CI 2.84–4.53), the long-term cumulative risk 6.35% (95% CI 4.69%–8.01%, mean 20.13 years) and the cumulative fatal stroke/CHD risk ratio 1.5:1. Important risk factors for long-term fatal CVD (RR, 95% CI) were male gender (1.49, 1.36–1.64), age over 60/65 years (7.55, 5.59–10.19) and current smoking (1.68, 1.26–2.24). High non-HDL-c, and β - and γ -tocopherol serum were associated only with CHD (HR 2.46 [95% CI 1.29–4.71] and 2.47 [1.10–5.61] respectively), while stage 1 and 2 hypertensions were associated only with fatal stroke (2.02 [1.19–3.44] and 2.89 [1.68–4.96] respectively).

Conclusions: Over a 10 year + follow-up period Asian subjects had a higher risk of stroke than CHD. Contrary to CVD prevention in Western countries, strategies should also consider stroke instead of CHD only.

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Asia; cardiovascular disease; coronary heart disease; long-term risk; risk factor; stroke

Introduction

Despite declining trends in fatal cardiovascular disease (CVD), coronary heart disease (CHD) and stroke remain a significant cause of death and morbidity worldwide^{1,2}. Owing to the fact that most CVD events are not fatal anymore, the prevalence and burden of CVD is increasing further. To prevent or postpone CVD occurrence, high-risk subjects need to be identified earlier, allowing for early targeting of modifiable risk factors and treatments with (personalized) preventive medications^{3–6}. This is especially true for Asian countries where more than half of the world's population resides, and where CVD death is on the rise^{7,8}.

Most studies on Asian populations have traditionally focused on the occurrence and risk factors of CVD within a short-term period (≤ 10 years)^{9,10}. This may underestimate a long-term CVD risk (>10 year follow-up), especially when

detrimental behavioral and environmental factors may occur earlier in life and continue to go unmanaged^{11–14}. Furthermore, the majority of this research also stems from “developed” Western countries^{15–17}, where the risk of CHD is approximately four times higher than of stroke^{18,19}. This focus on CHD may not appropriately translate to CVD prevention in Asians. The current review aims to estimate the long-term CVD burden and risk factors.

Methods

Study design

The protocol for this review was registered with PROSPERO (Reference CRD42016042939). This report was written based on a MOOSE checklist²⁰.

CONTACT Sylvi Irawati sylviirawati.2010@gmail.com Rijksuniversiteit Groningen, Groningen Research Institute of Pharmacy, Antonius Deusinglaan 1, Groningen 9713 AV, Netherlands

Supplemental data for this article can be accessed [here](#).

Search strategy

A search strategy was developed by S.I., E.H., B.W. and librarians (K.S., S.W.) ([supplemental online material](#)). S.I. conducted the search through PubMed, Embase and Web of Science on 12 July 2016. A web-based reference manager, RefWorks, was used to identify and eliminate duplicate studies. Predetermined inclusion criteria were applied in title/abstract and full-text screenings by S.I. and R.W. independently. Authors of the original studies were contacted to obtain any required information. In both screenings, the interrater agreement for study inclusion was assessed using Cohen's kappa (κ). Any disagreements between review authors were resolved by discussion. A third review author (E.H. or B.W.) was consulted when no agreement was reached after discussion.

Study selection

To obtain long-term incidence rates in the general population, only cohort studies were included. All types of review, meta-analyses, randomized controlled trials, cross-sectional studies, case series, case reports, editorials, letters and commentaries were excluded. We focused on Asian healthy adults (aged ≥ 18 years) from the general population. Subjects were free from CVD, i.e. had no history of myocardial infarction (MI) or stroke, at the start of the study. Only studies with a follow-up period of more than 10 years were included. Studies investigating only males or females, participants with a specific condition or disease, or occupational-based cohort were excluded.

The primary outcomes of interest were fatal and non-fatal CVD events. Secondary outcomes included any CHD and stroke incidences, fatal CHD, fatal stroke, and all-cause mortality. Only studies which defined their outcomes similarly or using the International Statistical Classification of Diseases (ICD) from the World Health Organization (WHO) were included.

Data extraction, risk of bias assessment and statistical analysis

To describe absolute risks, both rates and proportion with a 95% confidence interval (CI) were calculated for each outcome. The measure of association between risk factors and each outcome was presented as a pooled relative risk (RR), also with 95% CI. Forest plots were created using Microsoft Office Excel 2010²¹ and Review Manager (RevMan) version 5.3. (2014). Publications using the same existing data set were consolidated into a single record, with data preferentially extracted based on the longest period of follow-up. S.I. extracted data while R.W. and A.I. checked the correctness of the process.

The risk of bias of the included studies was assessed by S.I. and R.W. independently using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) ([supplemental online material](#))²². Disagreements were resolved

by discussion. A third review author (E.H.) was consulted when no agreement was reached after discussion.

In both descriptive and analytic meta-analyses, we used a random-effects model to calculate the pooled estimates²³. Heterogeneity across studies was evaluated using the Q-test (p value $\leq .10$ used as a cut-off point) and the I^2 statistic with 95% CI^{24–26}. When I^2 was $>50\%$, studies were subdivided based on the study duration.

Results

Study identification, study characteristics and risk of bias assessment

Of 1705 initial titles and abstracts, 1546 were excluded. After reviewing 159 full texts, 32 studies were included in the meta-analysis^{27–58} ([Figure 1](#), [Supplemental Online Material Table SI](#)). The strength of interrater agreement after both title/abstract and full-text screenings was satisfactory (agreement 92%, Cohen's kappa 0.43; 79%, 0.55, respectively). Most studies were from Japan (21 studies), followed by Taiwan (5), China (3), Israel (2) and Singapore (1). The duration of follow-up ranged from 11 to 29 years. Of 32 studies, 27 studies had started following their participants since the 1980s or 1990s, four since the 1960s or 1970s and only one since 2000. The participants' age ranged from 18 to 92 years. Of these studies, the risk of bias in one or more domains in 10 and 18 studies were considered high and unclear, respectively ([Supplemental Online Material Table SII](#)).

Primary outcomes: fatal and non-fatal cardiovascular disease events

The "average" (pooled-estimate) long-term rate of fatal CVD in the Asian populations was 3.68 per 1000 person-years (95% CI 2.84–4.53) ([Figure 2](#)). Studies from Singapore, Japan and Taiwan, all of which started their follow-up in the 1980s or 1990s, contributed to this number. Only the fatal CVD rate in Singapore (4.67 [4.52–4.81]) was above the average and the highest estimate.

The average cumulative fatal CVD over mean 20.13 years was 6.35% (95% CI 4.69%–8.01%) ([Supplemental Online Material Figure FI](#)). The highest cumulative fatal CVD was found in Taiwan, at 7.18% (95% CI 6.58%–7.77%) over mean 22.5 years, which was also the longest period of follow-up.

Secondary outcomes: any coronary heart disease and stroke incidences, fatal coronary heart disease, fatal stroke, and all-cause mortality

The average long-term incidence rate of any stroke was higher than fatal and non-fatal coronary events (3.14 per 1000 person-years [95% CI 2.12–4.16] vs. 1.51 [0.84–2.18]) ([Table 1](#)). The estimates for fatal and non-fatal coronary events were drawn from studies in the East-Asian populations (Japan and China) while those for any stroke events were only from Japan. Compared to the average estimates and to the Chinese, the Japanese had a higher incidence

Figure 1. Study selection flow.

rate of fatal and non-fatal coronary events. However, in Japan itself, both the incidence rate and cumulative incidence of any stroke were higher than fatal and non-fatal coronary events, even after excluding a study started in the 1960s⁵⁷ when the incidence of any stroke was still very high (3.14 per 1000 person-years [95% CI 2.12–4.16] vs. 1.72 [0.00–3.64]; 3.92% [3.35–4.48] vs. 2.23% [0.00–4.69]).

The long-term fatal rate of subcomponents of CVD was derived from three countries: Singapore, Taiwan and Japan (Table 2). Overall, the average long-term rate of fatal stroke was higher than fatal CHD (1.46 per 1000 person-years [95% CI 1.18–1.75] vs. 1.03 [0.26–1.81]). Singapore had above-average rates for fatal CHD (2.56 per 1000 person-years

[2.45–2.66]) while Taiwan had them for fatal stroke (1.8 per 1000 person-years [1.57–2.02]). This was also reflected in between-country comparisons. Singapore had the highest rate for fatal CHD and Taiwan had the lowest. In contrast, when the rate of fatal stroke was considered, the rank was the exact opposite. Specifically, the rate and cumulative estimate of fatal stroke in Japan and Taiwan were higher than those of CHD. The risks were opposite in Singapore.

The average long-term rate of all-cause mortality was 11.31 per 1000 person-years (95% CI 7.49–15.12) from Japan (five studies) and Taiwan (one study). Compared to the average, the risk in Japanese (10.87 [6.69–15.04]) was below while in Taiwanese (13.52 [12.91–14.13]) was above. The

Figure 2. Long-term (>10 years) rate of fatal cardiovascular disease in the Asian populations. Figure created using a tool from Someka.net.

same pattern was found in long-term cumulative all-cause mortality (Supplemental Online Material Table SIII).

Risk factors for long-term fatal and non-fatal cardiovascular disease events

Of the individual studies included in this review (Supplemental Online Material Table SI), risk factors of fatal CVD were still dominated by traditional variables such as: smoking^{29,52}, hypertension^{30,50,51}, overweight and obesity³¹. There was a synergistic effect between current smokers and each of these factors: hypertension, obesity and metabolic syndrome, which modified their effects on fatal CVD^{29,52}. Risk factors associated with long-term risks of fatal CHD and stroke were different, except for the use of incense (aromatic sticks release fragrant smoke when burned) in Singapore (HR 1.13 [95% CI 1.01–1.26] and 1.24 [1.06–1.45] for fatal CHD and fatal stroke, respectively)⁴⁷. Risk factors associated only with fatal CHD were non-fasting non-HDL-c ≥ 189 mg/dL (vs. ≤ 150 mg/dL)³², and β - and γ -tocopherol serum (HR 2.46 [95% CI 1.29–4.71] and 2.47 [1.10–5.61], respectively)³⁴. On the contrary, compared to normal blood pressure, stage 1 and 2 hypertension were significantly associated only with fatal stroke (HR 2.02 [95% CI 1.19–3.44] and 2.89 [1.68–4.96], respectively)⁵¹. Several protective factors also appeared to have contradictory effects on fatal CHD and fatal stroke. Non-fasting HDL-c 60–79 mg/dL (vs. 40–59 mg/dL) and high intake of fruit and vegetables were protective only against fatal CHD (HR 0.38

[95% CI 0.19–0.75] and 0.57 [0.37–0.87], respectively)^{28,46} while β -carotene serum, high intake of fruit, and per 10 $\mu\text{g}/\text{m}^3$ increase in particulate matter levels were only protective against fatal stroke (HR 0.60 [95% CI 0.37–0.98], 0.72 [0.54–0.95], 0.69 [0.59–0.82], respectively)^{34,44,46}.

Male gender, older age and current smokers were risk factors for fatal CVD (RR 1.49 [95% CI 1.36–1.64], 7.55 [5.59–10.19], 1.68 [1.26–2.24], respectively) (Figure 3). The risk of males compared to females in developing fatal CHD was higher than that in fatal stroke (RR 1.77 [95% CI 1.60–1.96] vs. 1.46 [1.28–1.68]). Additionally, the risk of suffering a fatal stroke among elderly compared to middle-aged people was higher than that of fatal CHD (RR 7.36 [95% CI 5.72–9.47] vs. 5.96 [4.17–8.52]).

Sensitivity and subgroup analysis

We conducted sensitivity analysis and subdivided studies based on duration of follow-up which resulted in non-significant heterogeneities (Supplemental Online Material Figure FII and FIII). Over a >20 year follow-up, the cumulative fatal stroke was higher than fatal CHD (4.18% [95% CI 3.48%–4.89%] vs. 1.57% [1.01–2.14]). The risks of suffering fatal CHD and fatal stroke were twice as high among males compared to females in a $\leq 15/20$ year follow-up. However, in the longer term, the risk of fatal stroke was slightly lower than of fatal CHD among males compared to females (RR 1.34 [95% CI 1.23–1.46] vs. 1.52 [1.04–2.22]).

Table 1. Long-term risk of fatal and non-fatal coronary and any stroke events in the Asian populations.

Authors	Country	Incidence rate per 1000 person-years (95% CI)		Cumulative incidence in % (95% CI)		Follow-up (years)
		Fatal and non-fatal coronary events	Any stroke events	Fatal and non-fatal coronary events	Any stroke events	
Livshits <i>et al.</i> 1989 ³⁹	Israel	not applicable	not applicable	13.29 (11.90–14.69)	not applicable	20
Ueda <i>et al.</i> 1988 ³⁷	Japan	not applicable	not applicable	not applicable	18.01 (15.95–20.08)	22
Turin <i>et al.</i> 2016b ⁵⁶	Japan	2.71 (2.33–3.08)	not applicable	3.50 (3.02–3.98)	not applicable	18
Nishiwaki <i>et al.</i> 2013 ⁴⁴	Japan	0.75 (0.69–0.81)	2.64 (2.53–2.75)	0.99 (0.92–1.07)	3.51 (3.36–3.66)	15
Turin <i>et al.</i> 2016a ⁵⁵	Japan	not applicable	3.68 (3.25–4.12)	not applicable	4.77 (4.21–5.34)	18
Matsumoto <i>et al.</i> 2010 ⁴⁰	Japan	not applicable	not applicable	not applicable	3.67 (3.33–4.00)	13
Pooled estimate (all Japan studies)		1.72 (0.00–3.64)	3.14 (2.12–4.16)	2.23 (0.00–4.69)	6.66 (5.01–8.31)	
Ren <i>et al.</i> 2010 ⁴⁸	China	1.18 (1.05–1.32)	not applicable	0.93 (0.82–1.04)	not applicable	15
Lin <i>et al.</i> 2013 ³⁶	Taiwan	not applicable	not applicable	not applicable	5.97 (4.91–7.02)	12
Lin <i>et al.</i> 2014 ³⁷	Taiwan	not applicable	not applicable	not applicable	3.78 (3.30–4.26)	11
Pooled estimate (all Taiwan studies)		not applicable	not applicable	not applicable	4.82 (2.68–6.96)	
Pooled estimate (studies with follow-up starting in 1980s/1990s)		same as average	same as average	1.69 (1.12–2.25) ^a	4.16 (3.62–4.71) ^b	
Pooled estimate (average, all studies)		1.51 (0.84–2.18) ^c	3.14 (2.12–4.16) ^d	3.83 (2.85–4.80) ^e	5.92 (4.73–7.11) ^f	

^aHeterogeneity: $Q = 15.87$, $df = 2$, $p \leq .10$, $I^2 = 87\%$ (64%–96%).

^bHeterogeneity: $Q = 8.82$, $df = 4$, $p \leq .10$, $I^2 = 55\%$ (0%–83%).

^cTotal person-years: 1,136,458.50; average follow-up: 16.00 years; heterogeneity: $Q = 5.93$, $df = 2$, $p = .05$, $I^2 = 66\%$ (0%–90%).

^dTotal person-years: 901,385.70; average follow-up: 15.00 years; heterogeneity: $Q = 1.00$, $df = 1$, $p = .32$, $I^2 = 0\%$.

^eTotal participants: 100,546; average follow-up: 17.00; heterogeneity: $Q = 83.28$, $df = 3$, $p \leq .10$, $I^2 = 96\%$ (93%–98%).

^fTotal participants: 90,285; average follow-up: 14.67; heterogeneity: $Q = 55.34$, $df = 5$, $p \leq .10$, $I^2 = 91\%$ (83%–95%).

Discussion

This study explored the risk of (non)-fatal CVD in Asian populations without prior CVD with follow-up of more than 10 years. Previously, the Asia-Pacific Cohort Study Collaboration (APCSC) and the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan Study (EPOCH-JAPAN) meta-analyses focused on CVD after a shorter follow-up period (≤ 10 years)^{10,59,60}. The APCSC included cohort studies mainly from China and Japan and single cohorts from Thailand, South Korea and Hong Kong while EPOCH-JAPAN only included Japanese cohorts^{9,59}.

Our study extends findings from these earlier studies to a 10 year + follow-up, where the average long-term cumulative incidence of fatal CVD, both in the Asian population as a whole (6.35% [95% CI 4.69%–8.01%], mean follow-up 20.00 years) and in Japanese alone (5.93% [3.68–8.23], mean follow-up 19.60 years) was around two times larger than the short-term risk found in APCSC (3.52% [3.47%–3.58%], median follow-up 6.1 years)¹⁰ and in EPOCH-JAPAN (2.89% [2.76–3.02], mean follow-up 10.2 years)⁶⁰.

Our analysis appears to support the assumption that the cumulative risk of long-term fatal CVD increases non-exponentially over time. A former study suggested that the 20 year risk of hard CHD should be at least twice the 10 year risk using a Framingham score approximation⁶¹. However, in the latter study, this “naïve” approach was proven to underestimate the true risk because it overlooked aging as an important factor of CVD. The most close estimation of long-term risk was a model which took competing risk of non-CVD death into account⁶². From two individual studies included in our review, the 20 year and lifetime risks of CHD and stroke (competing-risk adjusted) did not always increase linearly or exponentially in the Japanese. The most rapid increase of the 20 year and lifetime risks for both events compared to the 10 year risks occurred in the youngest index age group (45 years) and the leaps of increase were

getting smaller as index ages were getting older^{55,56}. The long-term risk of CVD also varied depending on gender and the burden of CVD risk factor(s)^{55,56,58}.

The average long-term cumulative incidence of subcomponents of CVD in the Asian populations was higher than the short-term risk, six times for fatal CHD (1.61% [95% CI 0.42%–2.81%] vs. 0.27% [0.25–0.28]) and four times for fatal stroke (2.42% [1.83–3.02] vs. 0.57% [0.55–0.59])¹⁰. However, in Japan, the risk was only almost two times higher than the short-term risk for both events (fatal CHD: 1.14% [0.65–1.64] vs. 0.58% [0.52–0.63], fatal stroke: 2.22% [1.16–3.29] vs. 1.36% [1.27–1.45])⁶⁰. Consistent with the short-term risk, the long-term risk of fatal stroke in the Asian population was also larger than that of fatal CHD. In our study, the long-term fatal stroke/CHD ratio was lower than the short-term ratio in Asians (1.5:1 vs. 2:1) similar to the Japanese (2:1)^{10,60}. Western subjects had an opposite fatal stroke/CHD ratio after both short-term (1:3)¹⁰ and long-term periods (e.g. around 1:4 in men and 1:2 in women, index age of 45 years with ≥ 2 major CVD risk factors)¹⁸. The relative importance of fatal stroke over fatal CHD on the long-term risk of fatal CVD in different populations was previously reported by Ancel Keys and co-investigators from the Seven Countries Study. Started 60 years ago in 1958, the study involved 16 cohorts of 12,763 men aged 40–59 years in seven countries. Of the 16 cohorts, one originated from the US, two were from Finland (eastern and western), one from the Netherlands (Zutphen), three from Italy (Crevalcore, Montegiorgio and Rome), two from Croatia (Dalmatia and Slavonia), three from Serbia (Velika Krsna, Zrenjanin and Belgrade), two from Greece (Crete and Corfu) and two from Japan (Tanushimaru and Ushibuka)^{63–65}. The 25 year age-adjusted stroke death rates in the US (36 per 1000) and most of Europe (Finland, Greece, Italy, Netherlands, Belgrade; range: 38–77 per 1000) were lower than Japan (83 and 107 per 1000), Serbia (94 and 119 per 1000) and Croatia (83 and 113 per 1000)⁶³. In contrast, the 25 year age-adjusted

Table 2. Long-term risk of fatal coronary heart disease and fatal stroke in the Asian population.

Authors	Country	Mortality of subcomponents of cardiovascular disease				Follow-up (years)
		Mortality rate per 1000 person-years (95% CI)		Cumulative mortality in % (95% CI)		
		Fatal CHD	Fatal stroke	Fatal CHD	Fatal stroke	
Hwang <i>et al.</i> 2011 ³¹	Taiwan	0.61 (0.48–0.73)	1.80 (1.57–2.02)	1.29 (1.01–1.56)	3.82 (3.35–4.29)	24
Brunner <i>et al.</i> 1987 ²⁷	Israel	not applicable	not applicable	5.69 (4.83–6.55)	not applicable	20
Pan <i>et al.</i> 2014 ⁴⁷	Singapore	2.56 (2.45–2.66)	1.33 (1.25–1.40)	3.79 (3.63–3.95)	1.96 (1.85–2.08)	18
Miyagawa <i>et al.</i> 2014 ⁴¹	Japan	0.89 (0.75–1.02)	2.16 (1.95–2.37)	1.86 (1.58–2.14)	4.54 (4.10–4.97)	24
Ito <i>et al.</i> 2016 ³²	Japan	0.57 (0.43–0.70)	0.92 (0.75–1.09)	1.03 (0.79–1.27)	1.67 (1.36–1.98)	20
Ito <i>et al.</i> 2006a ³³	Japan	not applicable	not applicable	not applicable	1.21 (0.82–1.60)	15
Ito <i>et al.</i> 2006b ³⁴	Japan	not applicable	not applicable	0.99 (0.63–1.34)	not applicable	15
Tanno <i>et al.</i> 2009 ⁵³	Japan	0.55 (0.50–0.60)	1.18 (1.11–1.25)	0.72 (0.66–0.78)	1.55 (1.45–1.64)	15
Pooled estimate (all Japan studies)		0.66 (0.47–0.86)	1.42 (0.85–1.98)	1.14 (0.65–1.64)	2.23 (1.16–3.29)	
Pooled estimate (studies with follow-up starting in 1980s/1990s)		same as average	same as average	1.61 (0.42–2.81) ^a	same as average	
Pooled estimate (average, all studies)		1.03 (0.26–1.81) ^b	1.46 (1.18–1.75) ^c	2.16 (1.01–3.31) ^d	2.42 (1.83–3.02) ^e	

^aHeterogeneity: $Q = 2.89$, $df = 5$, $p = .72$, $I^2 = 0\%$ (0%–72%).

^bTotal person-years: 2,250,168.30; average follow-up: 20.20 years; heterogeneity: $Q = 3.85$, $df = 4$, $p = .43$, $I^2 = 0\%$ (0%–78%).

^cTotal person-years: 2,250,168.30; average follow-up: 20.20 years; heterogeneity: $Q = 9.13$, $df = 4$, $p \leq .10$, $I^2 = 56\%$ (95% CI 0%–84%).

^dTotal participants: 157,920; average follow up: 19.43 years; heterogeneity: $Q = 8.35$, $df = 6$, $p = .21$, $I^2 = 28\%$ (0%–69%).

^eTotal participants: 155,007; average follow up: 19.33 years; heterogeneity: $Q = 16.85$, $df = 5$, $p \leq .10$, $I^2 = 70\%$ (31%–87%).

Abbreviation. CHD, coronary heart disease.

CHD death rates in the US and Europe (range: 118–202 per 1000), except in Dalmatia, were higher than Japan (45 and 63 per 1000) and Greece (46 and 95 per 1000).

This 25 year data from Japan was largely in agreement with our data, although there was a population difference and a large time difference between our included studies and this Seven Countries Study. Although the variety of investigated populations, especially with regard to Asians, was limited to Japan, the study still highlights different contributors to fatal CVD in different populations. The different pattern of CVD burden between Asian and Western populations might be translated into different risk factors which potentially require a different approach to the CVD prevention.

We only found a few short-term and no long-term follow-up studies investigating any possible differences between the two populations. In a short-term study (mean 4 years), among other factors (SBP, total cholesterol [TC], body mass index [BMI], diabetes and current smoking), only triglyceride (TG) was significantly different between the two populations ($p < .05$), with a stronger association with fatal CHD in Westerners (HR 1.66 [95% CI 1.33–2.07]) than in Asians (1.26 [1.12–1.41]). Interestingly, for subtypes of stroke, SBP was the only factor differing significantly between the two populations with a stronger association in Asians than in Westerners (fatal cerebral infarction: HR 1.44 [95% CI 1.35–1.54] vs. 1.36 [1.17–1.57]; fatal cerebral hemorrhage: 1.72 [1.63–1.82] vs. 1.49 [1.31–1.70])⁶⁶.

Based on individual studies included in our review, these same factors have different effects on developing CHD and stroke over a long-term period, e.g. non-fasting non-HDL-c ≥ 189 mg/dL and HDL-c 60–79 mg/dL were associated only with long-term fatal CHD (HR 2.46 [95% CI 1.29–4.71] and 0.38 [0.19–0.75], respectively) while stage 1 and 2 hypertension were associated only with long-term fatal stroke (HR 2.02 [1.19–3.44] and 2.89 [1.68–4.96], respectively). In short-term studies in Asian Pacific subjects, a lower level of one standard deviation (15.6 mg/dL) of HDL-c was associated only

with fatal or non-fatal CHD (HR not clearly reported)⁶⁷. However, hypertension was significantly associated with short-term risk of both fatal and non-fatal CHD, cerebral infarction, and cerebral hemorrhage (HR 2.47 [95% CI 2.16–2.82], 3.99 [3.32–4.80] and 9.26 [7.25–11.82])⁶⁸.

To summarize, three points are worth mentioning: 1) the risk of stroke is higher than CHD over a long-term period in Asians, 2) the limited evidence available showed a significant contribution of hypertension to the risk of developing CHD and stroke over a short-term period but only to the risk of stroke over a long-term period in Asians, and 3) the risk factors of developing CHD and stroke over a short-term period are different between Asians and Westerners while no evidence is available on the comparison of risk factors over a long-term period between the two populations. These points suggest that a different approach to CVD prevention may be needed. It is also worth noticing that most of the studies included and discussed here, both short-term and long-term studies, were conducted mainly in East Asian regions and in an era when the use of cardiovascular preventive medications was not highly promoted. Thus, this finding also reflects the lack of epidemiologic studies on CVD in other Asian regions, especially in lower-middle income countries, where CVD deaths take place the most.

The strengths of this review lie in its use of a comprehensive search strategy to include studies from all Asian countries and selection of only studies with more than 10 years of follow-up and with participants free of CVD at baseline, which enabled long-term absolute risk estimation. Prior studies relied on country death registries without specifying whether participants had already suffered from CVD at baseline^{69,70}.

Given the moderate to substantial degree of study heterogeneity ($I^2 = 50\%$ – 90%), we had to stratify our analyses. Another limitation is the difference in the start and end dates of the observation periods of the included studies. Those limitations were addressed by exploring regional and temporal variations, presenting the pooled estimate from

Figure 3. Meta-analysis of long-term risk factors for fatal and non-fatal cardiovascular disease, fatal coronary heart disease, fatal stroke, and all-cause mortality in the Asian populations.

studies started at the same period, and subgrouping studies based on duration of follow-up. Unavailable data for events in specific age groups also limits the standardization of (non)-fatal CVD rates which may overestimate or underestimate the burden depending on the structure of the study populations. The focus on English publications is another limitation; however, it is unclear whether language restriction may result in bias^{71,72}, for example some Asian countries explicitly publish research in English only⁷³. Due to the limited number of studies, it was not possible to formally address publication bias. We could only pool risk estimates for limited CVD risk factors because of the small number of studies investigating the same risk factors and the unavailability of individual participant data.

Conclusion

The long-term fatal CVD risk was almost double that of the reported short-term risk. Unlike Western populations, in the long term stroke risk remained larger than CHD risk. Male gender, older age and current smoking were important risk factors for long-term fatal CVD. Factors like non-HDL-c and HDL-c had different effects on long-term CHD and stroke, with hypertension being a more important predictor of long-term stroke risk than of short-term risk. Since most studies, even short-term studies, were from East Asian countries, there is limited information on both short-term and long-term burden, and risk factors of CVD, in other Asian countries. The different pattern of CVD risk and risk factors in Asian populations compared to Westerners asks for a different approach towards prevention.

Transparency

Declaration of funding

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Declaration of financial/other relationships

S.I., R.W., A.F.S., A.I., T.F., E.B., B.W. and E.H. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, Sylvi Irawati, upon reasonable request.

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