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Smoking and Elevated Blood Pressure Are the Most Important Risk Factors for Subarachnoid Hemorrhage in the Asia-Pacific Region

An Overview of 26 Cohorts Involving 306 620 Participants

Valery Feigin, MD, PhD; Varsha Parag, MSc (Hons); Carlene M. M. Lawes, MBChB, PhD; Anthony Rodgers, MBChB, FAFPHM, PhD; Il Suh, MD, PhD, FAHA; Mark Woodward, PhD; Konrad Jamrozik, MBBS, DPhil, FAFPHM; Hirotugu Ueshima, MD; on behalf of the Asia Pacific Cohort Studies Collaboration

Background and Purpose—The cause of subarachnoid hemorrhage (SAH) is poorly understood and there are few large cohort studies of risk factors for SAH. We investigated the risk of SAH mortality and morbidity associated with common cardiovascular risk factors in the Asia-Pacific region and examined whether the strengths of these associations were different in Asian and Australasian (predominantly white) populations.

Methods—Cohort studies were identified from Internet electronic databases, searches of proceedings of meetings, and personal communication. Hazard ratios (HRs) for systolic blood pressure (SBP), current smoking, total serum cholesterol, body mass index (BMI), and alcohol drinking were calculated from Cox models that were stratified by sex and cohort and adjusted for age at risk.

Results—Individual participant data from 26 prospective cohort studies (total number of participants 306 620) that reported incident cases of SAH (fatal and/or nonfatal) were available for analysis. During the median follow-up period of 8.2 years, a total of 236 incident cases of SAH were observed. Current smoking (HR, 2.4; 95% CI, 1.8 to 3.4) and SBP >140 mm Hg (HR, 2.0; 95% CI, 1.5 to 2.7) were significant and independent risk factors for SAH. Attributable risks of SAH associated with current smoking and elevated SBP (≥ 140 mm Hg) were 29% and 19%, respectively. There were no significant associations between the risk of SAH and cholesterol, BMI, or drinking alcohol. The strength of the associations of the common cardiovascular risk factors with the risk of SAH did not differ much between Asian and Australasian regions.

Conclusions—Cigarette smoking and SBP are the most important risk factors for SAH in the Asia-Pacific region. (*Stroke*. 2005;36:1360-1365.)

Key Words: meta-analysis ■ risk factors ■ subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) constitutes 4% to 7% of all strokes and, because of its high morbidity/mortality,¹⁻³ is one of the most devastating subtypes of stroke.⁴ Although previous studies have consistently indicated that cigarette smoking is the most important modifiable risk factor for SAH,⁵ the role of other common cardiovascular factors (eg, levels of blood pressure, serum cholesterol, body mass index [BMI], and alcohol intake) in the cause of SAH is poorly defined and the existing findings are controversial.⁶⁻⁸ The lack of knowledge on cause of SAH⁹ hampers its effective prevention. Stroke registry studies in the Asia-Pacific region indicate that the incidence of SAH is comparatively high in

Maori/Pacific¹⁰ and Japanese^{11,12} people but very low in China¹³ and India,¹⁴ suggesting that risk factors (or their prevalence and/or significance) for SAH in these populations may be different from those in other regions. However, few prospective data are available to provide reliable evidence to examine this hypothesis, and no direct comparisons have been made of the strength of the association of common cardiovascular risk factors with SAH endpoints in the different regions. Such information is crucial to estimating the burden of SAH attributable to common cardiovascular risk factors and, more importantly, the burden that is potentially avoidable with the control of these risk factors at the

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From the Clinical Trials Research Unit (V.F., V.P., C.M.M.L., A.R.), Department of Medicine and School of Population Health, Faculty of Medicine and Health Sciences, University of Auckland, New Zealand; the Department of Preventive Medicine (I.S.), Yonsei University College of Medicine, Seoul, Korea; The George Institute for International Health (M.W.), University of Sydney, Australia; the School of Population Health (K.J.), University of Queensland, Herston, Australia; and the Department of Health Science (H.U.), Shiga University of Medical Science, Shiga, Japan.

Correspondence to Valery Feigin, Clinical Trials Research Unit, Faculty of Medicine and Health Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand. E-mail v.feigin@ctr.u.auckland.ac.nz

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population level. These estimates may also contribute to understanding why the incidence rates of SAH in various countries are relatively steady^{1,15} despite changes observed in the prevalence of some common cardiovascular risk factors. In addition, international comparisons are not possible within individual cohort studies. Overviews, or meta-analyses, of cohort studies can overcome these issues.

We sought to estimate the mortality and morbidity from SAH associated with common cardiovascular risk factors in the Asia-Pacific region, and to determine if the strength and shapes of these associations with age and sex were different in Asian and Australasian (predominantly white; Australia and New Zealand) populations.

Participants and Methods

Identification of Studies and Collection of Data

The Asia Pacific Cohort Studies Collaboration (APCSC) is an individual participant data overview (meta-analysis) of cohort studies in the Asia-Pacific region. Methods of study identification and the characteristics of studies included have been reported elsewhere.¹⁶ In brief, studies were eligible for inclusion in the project if they satisfied the following criteria: (1) a study population from the Asia-Pacific region; (2) prospective cohort study design; (3) at least 5000 person-years of follow-up recorded; (4) date of birth or age, sex, and blood pressure recorded at baseline; and (5) date of death or age at death recorded during follow-up.

In addition, data sought on individual participants included total blood cholesterol, height, weight, cigarette smoking habit, and alcohol consumption. However, because these variables were not inclusion criteria for the collaboration, not all studies provided such data. Outcome data for this report included first-ever-in-a-lifetime SAH events (classified according to the ICD-9 code 430), whether fatal or nonfatal, that occurred during the follow-up period. Nonfatal events were defined as those that did not result in death within 28 days. In 7 studies (235 083 participants) that provided information, the diagnosis of SAH was based on CT/MRI scanning, brain autopsy, or cerebrospinal fluid examination in 84% of cases.

Statistical Analysis

Only those cohorts that provided data on baseline systolic blood pressure (SBP), blood cholesterol, BMI, smoking habit, and alcohol drinking were included in the analyses. All analyses were further restricted to participants aged 20 years or older. BMI was calculated as weight (kg) divided by the square of height (m). The available data only permitted analysis of smoking and alcohol drinking habits as categorical variables: current versus not current (includes former and never). For the Melbourne cohort, current drinkers included ever-drinkers. Analyses were undertaken for total (fatal and nonfatal) SAH events, and sensitivity analyses examined fatal SAH events only.

Stratified Cox proportional hazards analyses¹⁷ were used to regress time until first event against baseline cardiovascular risk factors. All analyses were stratified by sex and cohort to control for confounding and reduce statistical heterogeneity. Age at risk (age at the time of the event) was treated as an external time-dependent covariate¹⁸ to assess change in hazards as an individual's age increased. The hazard ratios and corresponding 95% CI for individual risk factors were adjusted for all other risk factors analyzed. Usual associations for SBP and cholesterol were estimated by adjusting for regression dilution bias.¹⁹ Repeat measurements of SBP and serum cholesterol available from 7 cohorts were used to estimate regression dilution factors (SBP=1.8 and cholesterol=1.7) using mixed models that took into account the varying time intervals between measurements.¹⁹

As well as examining SBP, cholesterol, and BMI on a continuous scale, these risk factors were divided into the following dichotomized groups (based on both sample sizes and clinical usefulness of

the levels); SBP, <140 and \geq 140 mm Hg; cholesterol, <4.5 and \geq 4.5 mmol/L; and BMI, <22 and \geq 22 kg/m². Attributable risks, adjusted for other risk factors, were calculated using population-attributable fractions^{20–22} for these categories and for current smoking and drinking. To assess the shape of the associations, additional analyses were conducted dividing baseline SBP, cholesterol, and BMI into the following quartiles: SBP (<115, 115 to 129, 130 to 144, \geq 145 mm Hg), cholesterol (<4.0, 4.0 to 4.9, 5.0 to 5.9, \geq 6.0 mmol/L), and BMI (<22.0, 22.0 to 23.9, 24.0 to 25.9, \geq 26.0 kg/m²). Ninety-five percent CIs for each quartile were estimated using the “floating absolute risk” method, which avoids the use of an arbitrary reference group.^{21,22}

Age-specific analyses included age at risk categories younger than 55 and 55 years or older, and analyses were also conducted by sex and region (Asia versus Australasia). Effect modification was assessed with the use of statistical interaction terms for age, sex, and region in the Cox model. Further sensitivity analyses investigated the impact of excluding the Korea Medical Insurance Corporation (KMIC) cohort study from the analyses, because it contributed the largest number of SAH events in this report, and cases diagnosed on clinical findings only.

Results

The analyses were based on 26 cohorts from APCSC that provided data on nonfatal and/or fatal SAH events and baseline SBP, cholesterol, BMI, smoking, and alcohol drinking habits (Table 1). In total, 306 620 participants contributed 1 898 565 person-years of follow-up. The Asian cohorts tended to have lower means than the Australasian cohorts for SBP, cholesterol, and BMI (Table 2). No significant differences in mean diastolic blood pressure levels were found between the Asian (78.9 SD 10.9 mm Hg) and Australasian (77.4 SD 12.1 mm Hg) cohorts. Proportionately more Asian participants were current smokers (except Asian women; sex-specific data not shown in Table 2) and fewer drank alcohol compared with Australasian participants.

Among the 5 risk factors analyzed, SBP and smoking were the only significant risk factors for total SAH events (Figure 1). Overall, the hazard ratio for SBP \geq 140 mm Hg was 2.0 (95% CI, 1.5 to 2.7), and that for current smoking was 2.4 (95% CI, 1.8 to 3.4). The significance of elevated SBP was more pronounced in younger subjects and in females compared with males. However, these differences were not statistically significant. The association between SBP and risk of SAH was not significantly different between Asian and Australasian subjects. The risk of total SAH increased steeply with level of SBP (Figure 2). Overall, a 10-mm Hg difference in SBP was associated with a 31% (95% CI, 23 to 38) difference in risk of total SAH. The hazardous effect of current smoking on the risk of total SAH occurrence was not dependent on age, sex, or region. The attributable risks associated with current smoking and elevated SBP (\geq 140 mm Hg) were 29% (95% CI, 21% to 35%) and 19% (95% CI, 13% to 24%), respectively.

No significant associations were found between cholesterol, BMI, or alcohol drinking with the risk of total SAH events (Figures 1 and 2). Overall, the hazard ratio for cholesterol \geq 4.5 mmol/L compared with <4.5 mmol/L was 0.9 (95% CI, 0.7 to 1.3), BMI \geq 22 kg/m² compared with <22 kg/m² was 1.0 (95% CI, 0.7 to 1.3), and current

TABLE 1. Characteristics of Cohorts

Country	Study Name	No.	Start Year	Median Follow-up, y	Female (%)	Baseline Age, y		Fatal SAH Events	Total SAH Events
						Mean	Range		
Japan	Aito Town	1109	1980	16.4	59	51	21–73	0	0
	Akabane	1830	1985	11.0	56	54	40–69	2	5
	Civil Service Workers	9217	1991	6.7	33	47	40–55	1	1
	Hisayama	1460	1961	25.1	56	56	40–91	19	26
	Konan	1188	1987	6.4	55	52	20–96	2	2
	Miyama	412	1988	6.6	62	59	41–80	0	0
	Ohasama	1872	1992	4.1	64	58	27–91	1	5
	Saitama	3582	1986	11.0	62	54	20–94	11	11
	Shibata	2308	1977	20.0	58	57	40–89	13	13
	Shigaraki Town	3641	1991	4.4	59	57	29–95	5	5
China	Fangshan	828	1992	2.7	67	47	34–72	0	0
	Guangzhou Occupational	4503	1987	7.9	32	43	29–87	0	0
	Huashan	1792	1992	2.8	52	53	35–76	0	0
	Seven Cities	6346	1987	2.7	57	58	35–91	3	5
	Six Cohorts	14 486	1982	8.4	48	45	35–59	2	4
	Yunnan	2626	1992	4.5	4	54	36–81	0	0
Taiwan	CVDFACTS	5525	1989	6.0	56	47	20–92	0	0
South Korea	KMIC	159 151	1992	4.0	33	44	35–59	22	106
Singapore	Singapore Heart	2277	1982	14.6	49	41	20–89	0	0
	Singapore NHS92	3302	1992	6.2	52	39	20–70	0	2
Australia	Australian National Heart Foundation	9100	1989	8.3	51	43	20–70	3	3
	Busselton	6997	1966	21.6	52	45	20–94	9	21
	Melbourne	41 122	1990	8.5	59	55	27–75	13	13
	Newcastle	5799	1983	8.7	50	52	21–77	0	0
	Perth	5981	1980	8.4	49	45	20–70	3	3
New Zealand	Fletcher Challenge	10 166	1992	5.8	28	44	20–89	5	11
Total or average*		306 620		8.2	45	48	20–96	114	236

*Averages weighted by person-years of follow-up (total person-years of follow-up was 1 898 565).

Zero events means that no SAH events were recorded during the follow-up period.

drinking compared with not drinking was 1.0 (95% CI 0.7 to 1.4). Confining analyses to fatal SAH events or to events with objective confirmation of hemorrhage, or excluding the KMIC cohort study (either from the overall data or just from the Asian data), or excluding studies with no SAH events did not statistically significantly alter our results.

Discussion

To our knowledge, this project is the first large-scale individual participant SAH data overview of risk factors for SAH in cohorts from the Asia-Pacific region. Overall, Asians tended to have lower means for SBP, cholesterol, and BMI, and fewer were alcohol drinkers, but there were more current male smokers compared with Australians and New Zealanders. This research extends findings from other epidemiological studies of SAH. First, we found that cigarette smoking and elevated SBP are the most important risk factors, each of which doubles the risk of SAH in the Asia-Pacific region. Whereas the hazardous effect of

cigarette smoking was strikingly consistent across all strata defined by age, sex, and region, the association with elevated SBP was more pronounced in younger subjects (younger than 55 years) and in women. Second, we detected no associations between the risk of SAH and cholesterol level, BMI, or alcohol drinking. Third, this is the first study to show that the associations of the common cardiovascular risk factors with the risk of SAH did not differ much between Asian and Australasian regions.

Major strengths and limitations of the APCSC study have been described elsewhere.^{23,24} In brief, the APCSC provides a large and unique set of individual participant database involving Asian cohorts and both men and women. The combination of data from a number of Asian and Australasian cohorts results in a relatively large number of SAH events, thus providing precise estimates of risk factor–SAH associations by region (Asia versus Australasia). Analyzing SBP, cholesterol, and BMI levels as categorical and continuous variables adjusted for each other and for regression dilution bias is a particular

TABLE 2. Mean (or Percentage) Values of Major Risk Factors by Region

Risk Factor	Asia	Australasia	Overall
SBP, mm Hg			
Mean (SD)	123.0 (16.6)	134.0 (20.6)	125.8 (18.4)
<140, no. (%)	192 547 (85)	52 753 (65)	244 300 (80)
Cholesterol, mmol/L			
Mean (SD)	4.9 (1.0)	6.6 (1.1)	5.1 (1.0)
<4.5, no. (%)	76 268 (34)	12 541 (16)	88 809 (29)
BMI, kg/m²			
Mean (SD)	22.9 (2.8)	26.4 (4.4)	23.8 (3.6)
<22, no. (%)	90 160 (40)	11 213 (14)	101 373 (33)
Smoking			
Current, no. (%)	85 188 (37)	14 440 (18)	99 628 (33)
Drinking alcohol			
Current, no. (%)	107 007 (47)	59 443 (75)	166 450 (54)

methodological strength of this study. Another important advantage is the high proportion of cases with objective confirmation of SAH, thus minimizing misclassification bias. However, we were not able to evaluate ethnic-specific associations of risk factors with SAH or to examine the association between different levels of cigarette smoking and alcohol drinking on the risk of SAH.

The absence of substantial gender differences in the significance of risk factors for SAH, the attenuation with age of the association with SBP, and the lack of a significant association between cholesterol levels and SAH are in line with our previous analyses on risk factors for intracerebral hemorrhage,^{23,24} suggesting some similarities in the pathogenesis of the 2 major subtypes of hemorrhagic stroke. The strong and positive association between baseline level of SBP and the risk of SAH concur with those found between “usual” level of SBP and the risk of ischemic stroke and intracerebral hemorrhage in the Asia-Pacific region.²³ Unlike previous findings of continuous positive relationships between baseline BMI and the risk of both ischemic stroke and intracerebral hemorrhage in

the Asia-Pacific region,²⁵ there were no such associations with SAH. Our findings did not support some other observations that lean BMI⁵ and low total cholesterol^{8,26} are associated with greater risk of SAH. Although it is possible that the low cutoff points used in our analyses may have contributed to the lack of the associations between BMI, total cholesterol, and SAH, sensitivity analyses using different cutoff points consistently found no associations. Strong positive associations between occurrence of SAH and smoking and elevated blood pressure but no significant associations with BMI, alcohol consumption, and total serum cholesterol in men were also found in the KMIC Study.⁷

Our results indicated that up to 19% of cases of SAH in the region were attributable to systolic blood pressure >140 mm Hg and 29% of cases of SAH were attributable to smoking. This suggests that a substantial proportion of SAH events could potentially be prevented by reducing blood pressure and smoking at a population level. Overall, each 10 mm Hg decrease in mean SBP is expected to result in a reduction in SAH of ≈31%. That the risk of SAH associated with SBP varies with age and gender has emphasized the importance of blood pressure control programs in young subjects (younger than 55 years) and in women. More generally, our findings of the significance of current smoking and elevated blood pressure as risk factors for SAH concur with results from other investigations in the Asia-Pacific region^{7,23,27,28} and elsewhere.⁶ Exposure to these risk factors individually and/or in combination promotes formation, growth, and rupture of intracranial aneurysm(s)^{29–31}—a major cause of SAH. The consistency of the data across studies involving different designs and populations suggests that cigarette smoking and elevated blood pressure are causally related to SAH.

Appendix Asia Pacific Cohort Studies Collaboration

Writing committee: V. Feigin, V. Parag, C.M.M. Lawes, A. Rodgers, I. Suh, M. Woodward, K. Jamrozik, H. Ueshima.

Statistical Analyses

V. Parag, R.B. Lin, S. Vander Hoorn, D.A. Bennett, F. Barzi, M. Woodward.

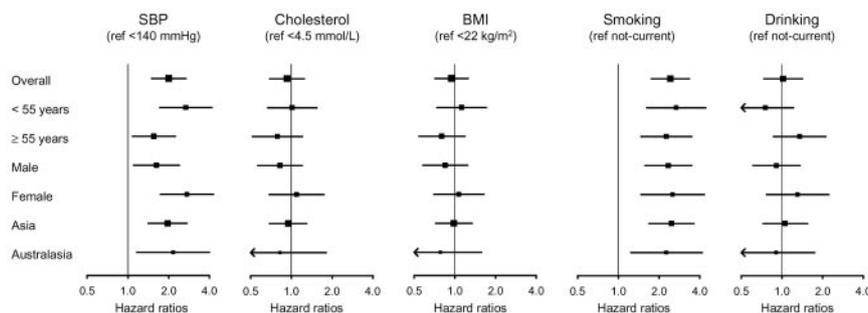


Figure 1. Dichotomized risk factor groups and the risk of total SAH events, overall and by age at risk, sex, and region subgroups. The hazard ratios for total SAH events adjusted for age at risk and stratified by sex and cohort, plotted on a log scale for 5 risk factors. The hazard ratios for individual risk factors were adjusted for all other risk factors analyzed and for regression dilution bias. The solid squares are drawn in proportion to the inverse of the variance, and the horizontal lines represent 95% confidence intervals. The risk factors have been dichotomized into the following groups: SBP, <140 (reference) and ≥ 140 mm Hg; cholesterol, <4.5 (reference) and ≥ 4.5 mmol/L; BMI, <22 (reference) and ≥ 22 kg/m²; and smoking and drinking, not current (reference) and current. For each risk factor, hazard ratios have been given overall and by age at risk, sex, and region subgroups.

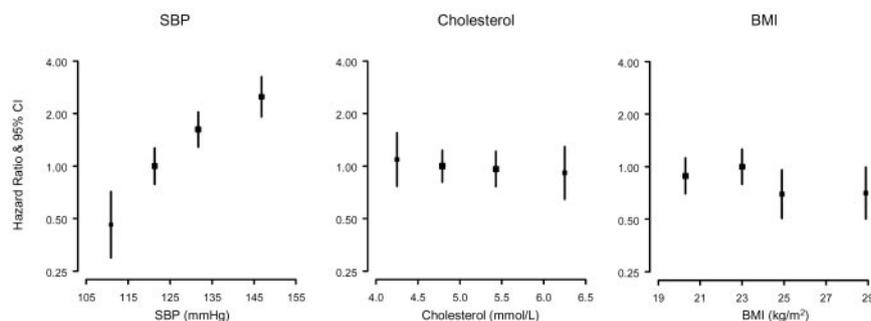


Figure 2. Continuous risk factors and the risk of total SAH events. The hazard ratio for total SAH events adjusted for age at risk and stratified by sex and cohort for each continuous risk factor which have been divided into the following groups: SBP (<115, 115 to 129, 130 to 144, \geq 145 mm Hg), cholesterol (<4.0, 4.0 to 4.9, 5.0 to 5.9, \geq 6.0 mmol/L), and BMI (<22.0, 22.0 to 23.9, 24.0 to 25.9, \geq 26.0 kg/m²). The x-axis coordinate for each group is the mean usual follow-up value for SBP and cholesterol and mean baseline value for BMI. The 95% confidence intervals for the hazard ratios are calculated using the floating absolute risk method with the second group as the reference. Other conventions as in Figure 1. SBP indicates systolic blood pressure; BMI, body mass index.

Executive Committee

D.F. Gu, T.H. Lam, C.M.M. Lawes, S. MacMahon, W.H. Pan, A. Rodgers, I. Suh, H. Ueshima, M. Woodward.

Participating Studies and Principal Collaborators

Aito Town: A. Okayama, H. Ueshima; *H. Maegawa*: *Akabane*: N. Aoki, M. Nakamura, N. Kubo, T. Yamada; *Anzhen02*: Z.S. Wu; *Anzhen*: C.H. Yao, Z.S. Wu; *Australian Longitudinal Study of Aging*: G. Andrews; *Australian National Heart Foundation*: T.A. Welborn; *Beijing Aging*: Z. Tang; *Beijing Steelworkers*: L.S. Liu, J.X. Xie; *Blood Donors' Health*: R. Norton, S. Ameratunga, S. MacMahon, G. Whitlock; *Busselton*: M.W. Knuiman; *Canberra-Queanbeyan*: H. Christensen; *Capital Iron and Steel Company*: X.G. Wu; *CISCH*: J. Zhou, X.H. Yu; *Civil Service Workers*: A. Tamakoshi; *CVDFACTS*: W.H. Pan; *East Beijing*: Z.L. Wu, L.Q. Chen, G.L. Shan; *Electricity Generating Authority of Thailand*: P. Sritara; *Fangshan*: D.F. Gu, X.F. Duan; *Fletcher Challenge*: S. MacMahon, R. Norton, G. Whitlock, R. Jackson; *Guangzhou*: Y.H. Li; *Guangzhou Occupational*: T.H. Lam, C.Q. Jiang; *Hisayama*: M. Fujishima, Y. Kiyohara, H. Iwamoto; *Hong Kong*: J. Woo, S.C. Ho; *Huashan*: Z. Hong, M.S. Huang, B. Zhou; *Kinmen*: J.L. Fuh; *Konan*: H. Ueshima, Y. Kita, S.R. Choudhury; *KMIC*: I. Suh, S.H. Jee, I.S. Kim; *Melbourne*: G.G. Giles; *Miyama*: T. Hashimoto, K. Sakata; *Newcastle*: A. Dobson; *Ohasama*: Y. Imai, T. Ohkubo, A. Hozawa; *Perth*: K. Jamrozik, M. Hobbs, R. Broadhurst; *Saitama*: K. Nakachi; *Seven Cities*: X.H. Fang, S.C. Li, Q.D. Yang; *Shanghai Factory Workers*: Z.M. Chen; *Shibata*: H. Tanaka; *Shigaraki Town*: Y. Kita, A. Nozaki, H. Ueshima; *Shirakawa*: H. Horibe, Y. Matsutani, M. Kagaya; *Singapore Heart*: K. Hughes, J. Lee; *Singapore NHS92*: D. Heng, S.K. Chew; *Six Cohorts*: B.F. Zhou, H.Y. Zhang; *Tanno/Soubetsu*: K. Shimamoto, S. Saitoh; *Tianjin*: Z.Z. Li, H.Y. Zhang; *Western Australia AAA Screenees*: P. Norman, K. Jamrozik; *Xi'an*: Y. He, T.H. Lam; *Yunnan*: S.X. Yao. (The underlined studies provided data used in this report.)

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