Review Article

Body mass index and risk of diabetes mellitus in the Asia-Pacific region

Asia Pacific Cohort Studies Collaboration¹

Few prospective data from the Asia Pacific region are available relating body mass index to the risk of diabetes. Our objective was to provide reliable age, sex and region specific estimates of the associations between body mass index and diabetes. Twenty-seven cohort studies from Asia, New Zealand and Australia, including 154,989 participants, contributed 1,244,793 person-years of follow-up. Outcome data included a combination of incidence of diabetes (based on blood glucose measurements) and fatal diabetes events. Hazard ratios were calculated from Cox models, stratified by sex and cohort, and adjusted for age at risk and smoking. During follow-up (mean = 8 years), 75 fatal diabetes events and 242 new cases of diabetes were documented. There were continuous positive associations between baseline body mass index and risk of diabetes with each 2 kg/m^2 lower body mass index associated with a 27% (23-30%) lower risk of diabetes. The associations were stronger in younger age groups, and regional comparisons demonstrated slightly stronger associations in Asian than in Australasian cohorts (P = 0.04). This overview provides evidence of a strong continuous association between body mass index and diabetes in the Asia Pacific region. The results indicate considerable potential for reduction in incidence of diabetes with population-wide lowering of body mass index in this region.

Key Words: Body mass index, obesity, diabetes mellitus, Asia

Introduction

Secular data indicate that overweight and obesity are increasing rapidly throughout the Asia Pacific region, due in part to increasing motorisation resulting in reduced physical activity and increased availability of energy-dense processed foods.2,3 Cohort studies in North America have shown consistently that risk of diabetes mellitus (DM) increases continuously with increasing body mass index (BMI).47 There is also evidence from Europe that intentional weight loss results in a marked reduction in incidence of DM.8 However, few comparable data are available for the Asia Pacific region and there is a recognised need for region-specific prospective analyses to determine the relationship between BMI and risk of developing comorbidities such as DM in Asian populations. The aim of these analyses was to investigate the association of BMI with mortality and morbidity due to DM in the Asia-Pacific region, and to determine if the strengths of these assoiations varied according to age, sex and region (Asia versus Australasia).

Methods

Identification of studies and collection of data

The Asia Pacific Cohort Studies Collaboration (APCSC) is an individual participant data overview (meta-analysis) involving prospective cohort studies in the Asia Pacific region. Methods of study identification, and characteristics of studies included have been reported elsewhere. ¹⁰ In brief, studies were eligible for inclusion in the collaboration if they satisfied the following criteria; 1) a study population from the Asia Pacific region: 2) prospective cohort study design; 3) at least 5,000 person-years of follow-up recorded; 4) date of birth or age, sex, and blood pressure recorded at baseline; 5) date of death or age at death recorded during follow-up. Studies were identified

by literature searches (Medline and EMBASE), scrutiny of abstracts from proceedings of meetings, and enquiry among collaborators and colleagues. There were no language restrictions. In addition to the above inclusion criteria, data sought on individual participants included history of DM, blood glucose, height, weight, and smoking habit. However, these variables were not essential data for inclusion in the collaboration so not all studies involved could contribute to the analyses reported here. Outcome data included fatal DM events and incidence of DM. Fatal DM events were those deaths coded to code 250 in the International Classification of Diseases (9th Revision) based on the underlying cause reported on the death certificate. Incidence of DM was identified by a single fasting blood glucose level >7 mmol/L (126 mg/dL) or a single nonfasting blood glucose level ≥ 11.1 mmol/L (200 mg/dL) in accordance with the American Diabetes Association guidelines for epidemiological studies.11 All data provided to the secretariat were checked for completeness and consistency and recoded where necessary to maximise comparability across cohorts. Summary reports were referred back to principal investigators of each collaborating study for review and confirmation.

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Statistical analysis

Only those cohorts that provided data on fatal DM during follow-up and baseline BMI, history of DM, and smoking (coded as never smokers, ex-smokers, current smokers) were included in the analyses. Analyses were further restricted to participants aged 20 years or more, who had no reported history of DM at baseline, or whose baseline blood glucose levels were below the threshold for diagnosis of DM. 11 BMI was calculated as weight (kg) divided by the square of height (m). Data from participants with a BMI of less than 12 kg/m² (N = 8) or greater than 59 kg/m^2 (N=4) were excluded from analysis. Outcomes examined included all DM events (incidence of DM and fatal DM events combined), incidence of DM alone, and fatal DM events alone. Separate analyses were conducted on the subset of cohorts that provided baseline and repeat blood glucose measurements.

A hypothesis of proportional hazards was tested and stratified Cox proportional-hazards analyses¹² were used to regress time until first event against baseline BMI using individual participant data collected on all cohorts. Time until first event was calculated as time between baseline and either death due to DM or first blood glucose measurement indicative of DM. 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 timedependent covariate12 in order to assess change in hazards as an individual's age increases. Smoking (never, ex and current) was also included as a covariate in all analyses. The hazard ratios and corresponding 95% confidence intervals were estimated for a 2 kg/m² reduction in BMI. As well as examining BMI on a continuous scale, participants were divided into quintiles according to baseline BMI (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, and ≥ 30 kg/m²) and hazard ratios were plotted against mean BMI. Ninety-five percent confidence intervals for each exposure group were estimated using the "floating absolute risk" method in order to provide a confidence interval for the reference group. 12,13 Age specific analyses included age at risk categories of <60, 60-69, ≥70 years, and analyses were also conducted by sex, and region (Asia vs. Australasia). Effect modification was assessed with the use of statistical interaction terms for sex and region in the Cox model.

Results

Study population

Analyses were based on data from 27 of the total 46 APCSC cohorts that provided fatal DM events and baseline BMI, history of DM and smoking habit (Table 1). Of the 27 cohorts included, 10 studies were from Japan, four from mainland China, two from Taiwan, one from Hong Kong, two from Singapore, seven from Australia, and one from New Zealand. In total, 154,989 participants contributed 1,244,793 person-years of follow-up and the mean duration of follow-up was eight years. The mean age of the participants at baseline was 53 years and 46% were female. Overall, 19% of participants were from Japan, 14% from mainland China, 9% from elsewhere in

Asia (Singapore, Taiwan and Hong Kong), and 57% were from Australasia (Australia and New Zealand). The overall mean (SD) baseline BMI was 24.7 (3.8) kg/m², with a mean BMI of 22.5 kg/m² in the Asian population and 26.3 kg/m² in the ANZ populations.

Body mass index and risk of diabetes

Three of the 27 cohorts recorded repeat blood glucose measurements (as well as providing data on fatal DM, and baseline BMI, history of DM and smoking): one from Japan, one from Australia and one from New Zealand (Table 1). Within these three cohorts (16,621 participants), 242 people had blood glucose measurements indicative of incidence of DM during follow-up while 75 people suffered a fatal DM event. Time intervals between baseline and repeat blood glucose measurements ranged from 0.7 to 29 years across these cohorts. Analyses limited to the three cohorts showed strong continuous relationship between increasing BMI and risk of total DM events (Fig. 1). On average, each 2-kg/m² lower BMI was associated with a 27% (23-30%) lower risk of total DM. A sensitivity analysis was also conducted excluding data from the Australian study, which dominated the overall analysis in terms of numbers of events. This confirmed the robustness of the original analysis and indicated that each 2-kg/m² lower BMI was associated with a 32% (23-40%) lower risk of total DM.

Each 2kg/m² lower BMI was associated with a 23% (15-30%) lower risk of total DM in men and 27% (23-31%) lower risk in women (P for homogeneity = 0.26) (Fig. 2). Age-specific associations of BMI and risk of total DM were also estimated (Fig. 2), showing stronger proportional associations in younger age groups. Each 2kg/m² lower BMI was associated with a 31% (25-37%) lower risk in total DM in those aged less than 60 years and 19% (11-26%) in those aged over 70 years (Fig. 2). The mean age at DM event was slightly higher in Australasia (66.3 years) than in Asia (61.8 years, P =0.0009). This would tend to produce apparently stronger overall associations between BMI and DM in Asian populations, since associations are steeper in the young (Fig. 2). Region-specific analyses demonstrated significant differences between Asia and Australasia in the size of the association between BMI and total DM. In the Asian cohort, each 2 kg/m² lower BMI was associated with a 37% (26-46%) lower risk of total DM and in Australasian cohorts the same reduction in BMI was associated with 25% (21-29%) lower risk, (P for homogeneity =

Effect of different outcome measures on observed associations

Within the full 27 cohorts, 75 participants suffered a fatal DM event and 313 participants had either a fatal DM event or developed DM during follow-up. Within the subset of three cohorts that recorded repeat blood glucose measurements, 242 people developed DM during follow-up based on glucose measurements only (incidence of DM). A consistent relationship between BMI and risk of DM was evident independent of the outcome measure used (Fig. 3).

Table 1. Characteristics of cohorts

Negron	Study name	Z	Start	Mean	%	Baseline age	age :	Baseline BMI	BMI	Fatal DM	New cases
			year	dn-wolloj	Females	(years)	(s	(kg/m^2)	رگ	Events	of DM
			:	(years)		Mean	SD	Mean	SD		
Japan	Aito Town	1,089	1980	15.3	09	51	10	22.9	3.1	2	
•	Akabane†	1,806	1985	11.2	56	54	8	22.5	3.0	-	46
	Civil Serivce Workers	6,077	1991	6.5	33	47	5	22.5	2.7	_	ı
	Konan	1,160	1987	6.3	56	52	16	21.9	3.0		
	Miyama	971	1988	6.3	26	99	10	22.2	3.0	-	ś
	Ohasama	1,975	1992	4.2	92	59	12	23.2	3.1	0	ı
	Saitama	3,530	1986	10.2	62	54	12	22.4	2.9	0	
	Shibata	2,308	1977	16.0	58	57	11	22.4	3.0	en	•
	Shigaraki Town	3,513	1991	3.8	99	57	14	22.5	3.1	0	ı
	Shirakawa	4,600	1974	16.7	54	48	12	21.5	2.8	ന	,
Mainland China	Beijing Aging	2,008	1992	4.4	20	70	6	23.2	3.9	3	ı
	CISCH	2,109	1992	3.3	51	44	7	24.7	3.5	0	1
	Seven Cities	10,573	1987	6.1	54	54	12	22.6	3.7	1.2	•
	Yunnan	6,545	1992	4.4	æ	99	6	21.6	2,9	2	1
Hong Kong	Hong Kong	2,610	1985	2.3	57	78	7	21.8	3.9		
Taiwan	CVDFACTS	5,563	1989	6.4	26	47	15	23.5	3.4	6	E
	Kinmen	1,079	1993	2.8	47	63	6	23.3	3.4	0	ı
Singapore	Singapore Heart	2,088	1982	12.7	20	39	13	23.3	4.2	0	•
	Singapore NHS92	2,984	1992	6.2	52	38	12	22.9	4.0	0	•
Australia	Australian Longitudinal Study of Aging	1,435	1992	4.9	49	78	9	26.0	4.1	0	•
	Australian National Heart Foundation	060,6	1989	8.2	51	43	13	25.3	4.2	0	
	Busselton [†]	4,766	1975	21.0	52	46	16	24.7	3.8	13	188
	Melbourne	39,935	1990	8.6	59	22	6	26.8	4.4	12	•
	Newcastle	3,331	1988	0.9	51	53	11	27.1	4.6	1	•
	Perth	10,009	1979-94	13.0	48	45	13	25.2	3.9	7	
	Western Australia AAA Screenees	10,786	1996	3.2	0	72	4	26.7	3.7	m	1
New Zealand	Fletcher Challenge [†]	10,049	1992	5.7	28	44	15	26.4	4.1	0	∞
Total or average*		154,989		8.0	46	51	11	24.7	3.8	75	242
New cases of DM are years of follow-up; to	New cases of DM are made up of repeat fasting blood glucose level ≥ 7 years of follow-up; total person years of follow-up=1,244,793; *cohorts		repeat non-fa	mmol/L or a repeat non-fasting blood glucose level ≥ 11.1 mmol/L; '.' = cohort did not record this information; *weighted by person that provided data on reneat blood glucose measurements (all cohorts provided fatal DM events and baseline BMI, history of DM	ose level ≥11. e measuremen	.1 mmol/L; '- ts (all cohort	: = cohort s provided	did not recor I fatal DM ev	d this info	ormation; *we	ighted by pers

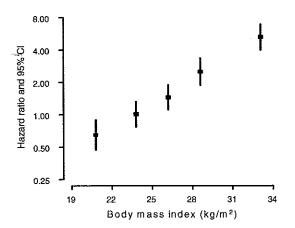


Figure 1. Body mass index and risk of diabetes. The hazard ratios for total diabetes event adjusted for age, sex, cohort and smoking habit are plotted on a log scale against BMI for each of the five groups defined by baseline BMI (<22.5, 22.5-24.9, 25.0-27.4, 27.5-29.9, and ≥ 30 kg/m²). The x-axis co-ordinate for each group is the mean baseline BMI. The 95% confidence intervals for the y-axis co-ordinate, hazard ratios, are calculated as floating absolute risks with the BMI group 22.5-24.9 kg/m² as the reference. The solid squares are larger where there are more events, as their size is proportional to the inverse variance, and the vertical lines represent 95% confidence intervals. Analysis was restricted to the three cohorts that provided data on repeat blood glucose measurements.

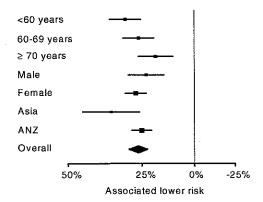
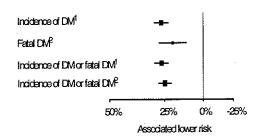


Figure 2. Associations of 2kg/m2 lower body mass index and risk of diabetes, by age, sex and region. The hazard ratios and 95% confidence intervals for body mass index are plotted separately for age, sex and region subgroups. Analysis was restricted to the three cohorts that provided data on repeat blood glucose measurements. Other conventions as in Figure 1.



¹subset of 3 cohorts that provided data on repeat blood glucose measurements ² full 27 cohorts

Figure 3. Associations of 2kg/m2 lower body mass index and risk of diabetes, by outcome measure. The hazard ratios and 95% confidence intervals for body mass index are plotted separately for various diabetes outcome measures. Other conventions as in Figure 1.

Discussion

This overview of prospective cohort studies provides the most reliable estimates to date of the associations between BMI and incidence of DM in the Asia Pacific region. The main findings were continuous positive associations between BMI and risk of DM that continued down to a baseline BMI of approximately 21 kg/m², were age-dependent, and were stronger in Asian than in Australasian cohorts.

This study has several strengths: it involves a large number of participants, utilises individual participant data, and weight and height were largely measured rather than self-reported (88% of cohorts who reported method of measurement indicated that they were measured). However, limitations in outcome measurement will undoubtedly have resulted in underestimation of the actual incidence of DM during follow-up. Provision of data on incidence of DM was not a requirement for participation in the Collaboration so many cohorts did not collect or provide data on this outcome and therefore our main analyses were based on data from three cohorts who provided data on repeat blood glucose measurements allowing diagnosis of new cases of diabetes. Incidence of DM was also based on a single measurement of blood glucose, which may have led to slightly lower estimates of incidence than would be obtained by using a combination of glucose measurement and medical history.11 Finally, while all 27 cohorts recorded cause of death there is likely to have been significant under-reporting of deaths from DM with many being coded to other related causes such as cardiovascular or renal disease. As such, the analyses reported in this paper should be regarded as preliminary although there are plans to collect additional data on DM incidence from the Collaboration and undertake more complete analyses in the future.

The prevalence of both obesity and DM in the Asia Paific region is increasing with economic development and changes from traditional to modernized lifestyle. In 1994, the estimated prevalence of DM was 2.5% in China (using the 1985 World Health Organization criteria), 14 a twofold increase compared with 1984 (0.9%). That crosssectional study also found that, on average, people with DM have a higher BMI than people with normal blood glucose levels. Similar patterns were apparent in the 1995 health survey in Korea, where 2.1% of males and 1.6% of females were found to have DM, and prevalence of DM increased with BMI.15 In Japan, it has been estimated that mean BMI in men is increasing by an increment of +0.44 kg/m² every 10 years. 16 Few prospective cohort studies have examined the association between BMI and DM in the region. A 6-year prospective study of 629 Chinese adults¹⁷ found a threefold increase in incidence of DM in those with a BMI of >27 compared with those of a BMI of $<24 \text{ kg/m}^2$ (52% versus 13%).

To date, most data on BMI and DM have been derived from North American cohort studies. The Nurses' Health Study has published several analyses examining the associations between BMI and DM, 4.18-20 all of which have shown that risk of DM increases with greater BMI and even women with a BMI below 25 kg/m² have an elevated risk. Other US studies have also reported similar findings in a variety of populations. 5-7 The relative risks

(RR's) for DM reported by these studies have been based upon arbitrary categories of BMI making comparisons difficult. Compared with women with a BMI of <23.0 kg/m² Hu et al., ⁴ reported a RR for DM of 20.1 (95% CI, 16.6 to 24.4) for women with a BMI of 30.0 – 34.9 kg/m². Compared with men with a BMI of <23.0 kg/m² Chan et al., ² reported a RR for DM of 11.6 (95% CI, 6.3 to 21.5) for men with a BMI of 31.0 – 32.7 kg/m². In contrast, we found that compared with men and women with a BMI of <22.5 kg/m², those with a BMI of >30 kg/m² had a RR of 8.1 (95% CI, 5.3 to 12.4).

There are some notable differences in study methodology that might explain these differences in results. The Nurses' Health Study and the Health Professionals' Follow-up Study used self-reported weights and heights to calculate BMI and also used self-reported incidence of diabetes as an outcome measure. The use of self-reported data for both exposure and outcome may lead to a systematic overestimation of RR's because the distribution of self-reported BMI is likely to be narrower than the distribution of actual BMI, and so the slope of the associations between BMI and risk of disease is artificially steep. If underreporting of diabetes is associated with BMI level, this could also result in bias in RR's away from the null. However, independent of methodology, all studies are consistent in finding a strong continuous linear association between BMI and risk of DM, which is evident from BMI levels well below 25 kg/m².

BMI is a generalised anthropometric measure that does not distinguish between weight associated with lean body mass and that associated with fat and it has been suggested that measures of central body fat or obesity such as waist circumference and waist-hip ratio may therefore be better predictors of diseases such as DM. Several prospective studies have found that waist-hip ratio and waist circumference provide important predictive information regarding risk of DM beyond that provided by BMI. ^{19,21-23} To date, there have been no prospective studies of this kind in the Asia-Pacific region. For the analyses reported in this paper it was not possible to evaluate the effect of waist circumference on risk of diabetes because data on waist circumference were not available for the relevant cohorts.

There is considerable debate about the need for different BMI cut-off points for determining overweight and obesity in Asian populations. At any given BMI, Asian populations have a higher percentage body fat compared with Caucasians²⁴ and so it has been suggested that ethnic-specific cut-off points for BMI are necessary. However, BMI cut points should be based on risk rather than percentage body fat and, to date, there are few region-specific prospective data to support an increased risk of disease at a lower BMI. Previous analyses did not demonstrate any significant differences in associations between BMI and cardiovascular disease between Asian and Australasian populations²⁵ In addition, a review of literature on associations between BMI and mortality does not support a lower cut point for Asians compared with Caucasians.²⁶ Although our analyses suggest that the risk of DM may be stronger in Asian than in Australasian populations, the Asian data were based on one Japanese cohort with relatively few events (47 in total) and thus should be interpreted cautiously. The regional differences observed may also have been due to the slightly lower mean age at DM event in Asia than in Australasia since associations were steeper in the young. What is clear, however, is that risk of DM increases continuously with BMI and that there is no practical lower threshold for risk in either Western or Asian populations.

Our results suggest that, rather than concentrating on individuals who are overweight or obese according to the traditional BMI cut-off levels, population-wide lowering of BMI should be the focus of weight reduction interventions. The benefits of such reductions are likely to be considerable: about one-quarter reduction in risk of DM for a 2kg/m² reduction in BMI. For an individual with a height of 1.7 m and a weight of 70 kg (BMI 24.2), such a reduction in BMI would equate to a weight reduction of approximately 6 kg. In addition, these results support the view that increasing BMI is a major risk factor for DM in both Asian and Australian/New Zealand populations.

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Appendix

Asia Pacific Cohort Studies Collaboration

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Review Article

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Asia Pacific Cohort Studies Collaboration¹

亚太地区的体质指数与糖尿病的危险度

亚太地区体质指数与糖尿病危险度间关系的前瞻性数据很少。我们的目的是对体质指数和糖尿病间的关联提供可靠的年龄、性别、地域特异性评估。来自亚洲、新西兰和澳大利亚的 27个群组研究,包括 154989 参与者,总共 1244793 人次的跟踪调查。得到的数据包括糖尿病的发生率(根据血糖测量)和糖尿病致死病例。危害比通过环氧化酶模型计算,根据性别和群组分级,并且对危险龄群和吸烟者进行调整。在跟踪调查中(平均为 8 年),有 75 例糖尿病致死病例和 242 例新病例被备案。体质指数基线和糖尿病的危险度有一致的正关联性,体质指数每降低 2 kg/m² 糖尿病的危险度就降低 27%(23-30%)。这个关联性在年轻组更加显著,而地域间的比较表明亚洲比澳洲群组略为显著(P=0.04)。这个综述证明亚太地区的体质指数和糖尿病间有高度一致关联性。结果暗示通过降低这个地区中群体范围的体质指数来降低糖尿病的发生率是相当有潜力的。

关键词:身体质量指数、肥胖、糖尿病、亚洲。