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MJM

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1. Standard Journal Article
Chua SK, Kilung A, Ong TK, Fong AY, Yew KL, Khiew NZ et al. Carotid intima media thickness and high sensitivity C-reactive protein as markers of cardiovascular risk in a Malaysian population. *Med J Malaysia* 2014; 69(4): 166-74.

Books and Other Monographs:

2. Personal Author(s)
Ghani SN, Yadav H. Health Care in Malaysia. Kuala Lumpur: University of Malaya Press; 2008.
3. Corporate Author
World Health Organization. World Health Statistics 2015. Geneva: World Health Organization; 2015.

4. Editor, Compiler, Chairman as Author
Jayakumar G, Retneswari M, editors. Occupational Health for Health Care Professionals. 1st ed. Kuala Lumpur: Medical Association of Malaysia; 2008.
5. Chapter in Book
Aw TC. The occupational history. In: Baxter P, Aw TC, Cockcroft A, Durrington P, Malcolm J, editors. Hunter's Disease of Occupations. 10th ed. London: Hodder Arnold; 2010: 33-42.
6. Agency Publication
National Care for Health Statistics. Acute conditions: incidence and associated disability, United States, July 1968 - June 1969. Rockville, Me: National Centre for Health Statistics, 1972. (Vital and health statistics). Series 10: data from the National Health Survey, No 69). (DHEW Publication No (HSM) 72 - 1036).

Online articles

7. Webpage: Webpage are referenced with their URL and access date, and as much other information as is available. Cited date is important as webpage can be updated and URLs change. The "cited" should contain the month and year accessed.

Ministry of Health Malaysia. Press Release: Status of preparedness and response by the ministry of health in and event of outbreak of Ebola in Malaysia 2014 [cited Dec 2014]. Available from: http://www.moh.gov.my/english.php/database_stores/store_view_page/21/437.

Kaos J. 40°C threshold for 'heatwave emergency' Kuala Lumpur: The Star Malaysia; [updated 18 March 2016, cited March 2016]. Available from: <http://www.thestar.com.my/news/nation/2016/03/18/heatwave-emergency-threshold/>.

Other Articles:

8. Newspaper Article
Panirchellum V. 'No outdoor activities if weather too hot'. the Sun. 2016; March 18: 9(col. 1-3).
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All original papers which are accepted for publication by the MJM, will be considered for the 'Best Paper Award' for the year of publication. No award will be made for any particular year if none of the submitted papers are judged to be of suitable quality.

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Foreword

Approximately three-quarters of deaths worldwide today are caused by non-communicable diseases (NCDs) such as cardiovascular disease, cancer, diabetes, chronic respiratory disease, and injury. Non-communicable diseases used to be the exclusive bane of high income countries, but now more than half of NCD deaths occur in low and middle-income countries. This means that these countries which still have to deal with communicable diseases, would also have to battle the health, social, and economic burden of lifestyle related diseases.

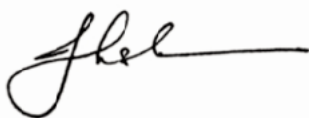
Although NCDs were not part of the 2000 Millennium Development Goals, in 2011, it became a focus with the United Nations and the World Health Organization calling for a 25% reduction in NCD-related mortality by the year 2025. Are we able to achieve this goal? Is the burden of NCDs in Malaysia overwhelming? How prevalent are the risk factors? And what are the issues in prevention, detection, and treatment that must be addressed? As many of the NCDs are of long duration and generally slow in progression, our strategies should also be long-term. But how do we improve health literacy and promote early detection? And how do we do all these cost-effectively?

The greatest of all mistakes is to do nothing because you think you can only do a little. This old quote that was popularised again by the American motivational coach, Zig Ziglar, is the sentiment that we should adopt. The problem and effect of NCDs appear overwhelming but the history of medicine has shown us that we are capable of taking on the challenge if we do our part.

The Clinical Research Centre, (CRC), once again collaborating with Assoc Prof Lim Kean Ghee from the International Medical University, has produced this sequel to 2014's Medical Journal of Malaysia (MJM) supplement of Malaysian Research on Major Diseases. This MJM supplement serves to reinforce NCDs as a major healthcare problem with a compilation of articles covering nine different conditions. Three reviews cover the critical risk factors - obesity, metabolic syndrome, and smoking. Four other reviews discuss common diseases, i.e. acute coronary syndrome, stroke, lung cancer, and rheumatic heart disease. This supplement also includes two topics which may not be as widely discussed or highlighted as the earlier conditions. The first is child abuse, an important cause of childhood morbidity. And the second focuses on occupational injury, which has high rates in developing countries.

To the authors of the reviews selected for this supplement, congratulations and thank you for taking the time to review the local research conducted in your field of expertise. I hope the reviews are continuously updated so that our recommendations and strategies remain evidenced-based and current. And I hope this encourages other specialties to also come up with their own reviews.

I also take this opportunity to applaud the behind-the-scene team who came together again to ensure that local research publications get their share of the limelight.



Datuk Dr. Noor Hisham Abdullah
Director-General of Health, Malaysia

Foreword

In my foreword for the Medical Journal of Malaysia (MJM) supplement on Malaysian Research on Major Diseases two years ago, I highlighted the importance of systematic reviews in generating a consensus on medical evidence and its implications on patient care. I am happy to see the Clinical Research Centre (CRC) continuing this tradition of reviewing local research with the production of this supplement.

The focus on non-communicable diseases (NCDs) is important as the prevalence of these conditions in Malaysia are rising substantially. The Ministry of Health has already implemented many NCD initiatives at national and local levels; and these include various publications such as survey reports, registry reports, factsheets, annual reports, national strategic plans, and guidelines. The publication of this supplement will add to this repository of information.

The nine conditions featured here have been extensively researched in Malaysia. For instance, the review on coronary artery disease, a primary cause of morbidity and mortality in Malaysia as it is elsewhere in the world, looked at data from over 100 local papers published in this disease area. The snapshots from the reviews in this supplement provide us an overview of the local state of the disease with a bibliography of the relevant papers which healthcare professionals can read further for an in-depth study.

Clinicians can use this MJM publication as reference to guide their treatment decisions, and get a perspective on what fellow clinicians see in their respective practices. Other healthcare professionals can also benefit by getting the latest information with a local flavour. Researchers can refer to this to identify patient profiles and risk factors, and discover where the next wave of research should be. Policymakers can also be better equipped to make important healthcare decisions when they have access to data from their own settings generated by their own clinicians. Therefore, I encourage clinical researchers to publish their data; and to those who already do, keep publishing to keep your data relevant. Without your publications, how would we know whether our treatment choices are effective and efficient? Or why a particular approach worked so well in one setting but not in another? Or whether a certain innovation is practical or cost effective? Or how to improve patient care and experience?

Finally, I thank all parties involved in this endeavour - the authors for searching, assessing, and summarising the research; and the editorial team for putting this supplement together. I encourage the CRC to continue producing thematic compilations like this, as clearly the reviews in this supplement feature research that matter to both healthcare professionals and patients. I look forward to the next compilation.



Datuk Dr Shahnaz Murad

Deputy Director-General of Health (Research and Technical Support), Malaysia

A Review of Adult Obesity Research in Malaysia

Lim Kean Ghee, FRCS

International Medical University Clinical School, Jalan Rasah, 70300 Seremban

ABSTRACT

A literature search of articles as detailed in the paper *Bibliography of clinical research in Malaysia: methods and brief results*, using the MESH terms Obesity; Obesity, Abdominal; and Overweight; covering the years 2000 till 2015 was undertaken and 265 articles were identified. Serial population studies show that the prevalence of obesity increased rapidly in Malaysia in the last decade of the twentieth century. This follows the rising availability of food per capita which had been begun two to three decades previously. Almost every birth cohort, even up to those in their seventh decade increased in prevalence of overweight and obesity between 1996 and 2006. However, the rise in prevalence in obesity appears to have slowed after the first decade of the twentieth century. Women are more obese than men and Malays and Indians are more obese than Chinese. The Orang Asli are the least obese ethnic group in Malaysia but that may change with socio-economic development. Neither living in rural areas nor having low income protects against obesity. On the contrary, a tertiary education and those in the highest income bracket are associated with less obesity. Malaysians are generally not physically active enough, in the modes of transportation they use and how they use their leisure time.

Other criteria and measures of obesity have been investigated, such as the relevance of abdominal obesity, and the Asian criteria or Body Mass Index (BMI) cut-offs value of 23.0kg/m² for overweight and 27.0 kg/m² for obesity, with the view that the risk of diabetes and other chronic diseases start to increase at lower values in Asians compared to Europeans. Nevertheless the standard World Health Organisation (WHO) guidelines for obesity are still most widely used and hence is the best common reference.

Guidelines for the management of obesity have been published and projects to combat obesity are being run. However, more effort needs to be invested. Studies on intervention programmes show that weight loss is not easy to achieve nor maintain.

Laboratory research worldwide has uncovered several genetic and biochemical markers associated with obesity. Similar studies in Malaysia have found some biomarkers with an association to obesity in the local population but none of great significance.

KEY WORDS:

overweight, obesity, Malaysia, abdominal obesity, physical activity, food intake, hypertension, diabetes, metabolic syndrome, psychiatric conditions, breast cancer, colorectal cancer

INTRODUCTION

265 articles were identified and examined in a literature search on adult obesity in Malaysia. The search using the medical subject headings (MeSH) Obesity; Obesity, Abdominal; and Overweight; followed the method that has been previously described.¹ In brief, clinical research publications containing data on Malaysia for the period Jan 2000 - Dec 2015 were included (last search date 2 Feb 2016). Conference proceedings (but not conference abstracts), relevant theses/dissertation, books/book chapters, reports and clinical practice guidelines were included. 365 articles were initially identified, but 100 articles pertaining to childhood and adolescent obesity were excluded.

Nutrition is vital for health. Undernourishment was a significant burden on human health in the past. However, human morbidity and mortality increases not only with undernourishment but also with excessive nutrition. Obesity, the disease of excessive adipose tissue is increasingly prevalent worldwide.

The WHO criteria for Body Mass Index(BMI) classifies a BMI of 25-29.9kg/m² as overweight and >30kg/m² as obese.² BMI does overestimate obesity in muscular individuals and underestimate it in such as the elderly who have lost body mass. However, it still is the most widely used index for obesity. Obesity is recognized as a major determinant of non-communicable diseases such as cardiovascular disease, cancers, type 2 diabetes mellitus, respiratory problems, gallbladder diseases, post-operative morbidity and musculoskeletal disorders such as osteoarthritis.

There has been a clearly documented dramatic increase in the prevalence of obesity in Malaysia over the last three decades since large scale population data became available. The rise of obesity is not a problem unique to Malaysia. In the global context, alongside development and prosperity, in many countries especially in Asia, obesity has become a leading health issue.

This process has been termed nutrition transition, from low availability of calories mainly in the form of plant products to diets high in fats, sugars and energy dense processed foods. This in turn has been the result of rapid economic development which has taken place in Malaysia in the last quarter of the twentieth century. Malaysia has recently been ranked second highest in East and Southeast Asia in terms of being overweight.³

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SECTION 1: REVIEW OF LITERATURE

PREVALENCE OF OBESITY

In the Adult* Population

There have been six large (>10,000 respondents) national population studies on the prevalence of obesity (Table I)

The National Health Morbidity Survey (NHMS II) in 1996 found that 16.6% prevalence of the adult population are overweight and 4.4% obese.⁴ (This study is often quoted as finding a prevalence 20.7% of individuals aged 20 years and older who were overweight and 5.8% obese).⁵ Six years later, the Malaysian Adults Nutrition Survey (MANS) carried out between October 2002 and July 2003,⁶ found that the prevalence of obesity had more than doubled and that the number of adults overweight increased more than 60%. If that rather rapid increase in the prevalence of obesity seemed hard to believe, the findings were confirmed in another study in 2004.⁷ Following shortly, the Third National Health and Morbidity Survey (NHMS III) in 2006 conducted among 33,055 adults found 29.1% were overweight and 14.0% obese.⁸ When the next NMHS was done five years later in 2011, it showed only a slight increase in the rates of those overweight and obese.⁹ The NHMS 2015 shows the prevalence of overweight plateauing (Table I) but is obesity still rising. This just means the number of people moving into the overweight category about equals the number of overweight people moving into the obese category.¹⁰ (Figure 1 and 2)

Age

The NSCVDRF study only reported data for obesity and not overweight. Leaving that study aside the other five large population nutritional surveys come at almost 5-year intervals. The MANS study is two years late in 2003 instead of 2001. The NMHS 2015 comes only 4 years after the NHMS 2011. Using these five large studies as a five year plots alongside each other for examination of the prevalence of overweight and obesity in the various age groups we can observe the trend on cohorts over time, albeit bearing in mind they are not all exactly five years apart.

The prevalence of both overweight and obesity are lowest among young adults but more than doubles to a peak in middle age (Figure 3 and 4). In the NHMS II in 1996, the peak age for obesity was the 40-49 year age band (Figure 4). In the NMHS III,⁸ which reported age in 5 year bands, the peak was the 50-54 year age band and in the NMHS 2011⁹ the peak had moved further to the 55-59 year band (Figure 4). It therefore appears that the cohort born between 1952-1957 carried the high peak of obesity with them as they aged. Although they are no longer the age group with the highest prevalence of obesity in 2015, having reached the 60-64 year band, their prevalence of obesity rose just slightly (Figure 6 bolder line).¹⁰ The cohort behind them aged 55-59 years became the age group with highest obesity.

Does the rising prevalence of obesity mean only the young age groups move up in age carrying their higher prevalence with them or did all age groups also increase in weight? Figures 5 and 6 which shows the prevalence of overweight and obese by birth cohorts shows us that every birth cohort

increased in prevalence of overweight and obesity between 1996 and 2006. Even the cohort born between 1927-1936 who were >60 years old in 1996 showed an increased in prevalence of overweight and obesity 10 years later in the NMHS III survey when they were the >70 year age group. (prevalence of overweight 15.6% rose to 21.1-29.3%, obesity 3.1% rose to 7.2-8.6%). It appears that the period between 1996 to 2006 saw the most rapid rise in weight gain in the Malaysian population.

However between 2006 and 2015, cohorts born before 1952, ie. those who were above 55 years old in 2006, appeared no longer to have increased in prevalence of overweight (Figure 5), but instead plateaued or even decreased slightly in prevalence.

The Elderly

As noted, from the age of about 60 years upwards, the prevalence of overweight and obesity declines. The prevalence of obesity declines more rapidly than overweight, reaching less than half the peak age value in the 70-75 year age group (Figure 4). The prevalence of overweight on the other hand stays up to 60-70% the peak age prevalence rates (Figure 3). **This may indicate the obese suffer a higher mortality rate. The decline in prevalence among those 80+ years is even more striking.** Their prevalence of obesity is only half that of the 75-79 year age group (Figure 4).

Suzana *et al.* have also noted that while a large proportion of the elderly may be overweight and obese, signs of malnutrition may be present among them^{11,12} (malnutrition will not be explored further in this review).

Sex

Consistently across the studies, **more women are obese than men**,^{4,6,7,8,9,10} but more men are overweight than women.^{4,6,7,8,9,10} Only among young adults are more men obese than women.^{6,14} By the late 20s women have overtaken men in obesity; the cause of this is usually attributed to weight gain after pregnancy. This greater prevalence of overweight among men was especially true among Chinese but among Indians more women are overweight compared to men.⁶ It appears that when women put on weight they 'go all the way'. Furthermore the gap between the prevalence of obesity between women and men has widened.^{4,8}

Three studies reported the prevalence of obesity by age and also by sex.^{4,6,7} In the NHMS II and NSCVDRF studies^{4,7} men appeared to have a peak age younger than women, but that is not clear in the MANS study.⁶

Suzana *et al.* have noted that elderly women are twice as obese as men, and by weight circumference (measure for abdominal obesity) women are three times as obese as men.^{11,12}

There have been several studies focusing specifically on women (Table III). Chee *et al.* found that the prevalence of overweight among women electronic factory worker for younger age groups were similar to the survey NHMS II done four years before, but older women electronic factory worker had higher overweight prevalence and mean BMI than the

* Unless otherwise stated, the adult population refers to those aged 18 years and above, and overweight and obesity are defined according to the WHO criteria of a BMI of 25-29.9kg/m² for overweight and >30kg/m² for obese.²

Table I: Sample size and prevalence of overweight and obesity of Large Malaysian Obesity Studies

	Sample Size	Prevalence of	
		Overweight*	Obesity*
National Health and Morbidity Survey II (NHMS II) 1996 ⁴	28,737	16.6% (20.7%#)	4.4% (5.8%#)
Malaysian Adults Nutrition Survey (MANS) 2003 ⁶	10,216	26.7%	12.2%
The National study on Cardio-Vascular Disease Risk Factors(NSCVDRF) 2004 ⁷	16,127		11.7%## (12.6%#)
Third National Health and Morbidity Survey (NHMS III) 2006 ⁸	33,055	29.1%	14.0%
National Health and Morbidity Survey 2011 (NHMS 2011) ⁹	28,498	29.4%	15.1%
National Health and Morbidity Survey 2015 (NHMS 2015) ¹⁰	18,499	30.0%	17.7%

Prevalence among 20 years and above## Prevalence among 15 years and above

Table II: Prevalence of Overweight and Obesity by sex

	Overweight (%)		Obese (%)	
	Men	Women	Men	Women
NHMS 1996	20.1	21.4	4.0	7.6
MANS 2003	28.6	24.8	9.7	14.7
NSCVDRF 2004			9.6	13.8
NHMS 2006	29.7	28.6	10.0	17.4
NHMS 2011	30.9	27.8	12.7	17.6
NHMS 2015	31.6	28.3	15.0	20.6

Table III: Prevalence of overweight and obesity among women in several localised studies

Author, year of study	Sample size	Age group (years)	Characteristics	Ethnicity (%)	Overweight	Obesity
Chee 2000 ¹⁵	1612	17-55	Women Electronic factory workers	Malays=78.5 Chinese=2.2 Indians=17.7	24.1	13.3
Sherina 2004 ¹⁷	972	20-59	Women in Selangor	Malays=54.9 Chinese=20.0 Indians=23.4		19.4 6.2 19.0
Poh 2006 ¹⁸	253	30-45	Women Teachers and civil servants in Kuala Lumpur	Malays=64.4 Chinese=26.1 Indians=9.5		53.4 28.8 66.7
Norsa'adah 2000 ¹⁹	175	20-70	Women with Breast Cancer, Kelantan	Malay=77.7 Chinese=20.6 Others=1.7	34.3	13.7
Yong ²⁰	368	20-75	Women with Breast Cancer, from 8 different Hospitals	Malay=57.1 Chinese=33.2 Indians=9.8	31.5	10.9
Lee ²¹	115	20-59	Women Office Workers, Kuala Lumpur and Selangor	Malays	33.0	22.6
Siti Affira ²²	215	18-55	Women in Corporate Companies, Petaling Jaya	Malays=81.9 Chinese=10.2 Indians=7.9	24.7	7.9
Lua 2011 ²³	41	24-68	Women with Breast Cancer, Terengganu and Kelantan	Malay=92.7 Chinese=7.3	29.1	12.2
Hasnah ²⁴	125	50-65	Women in Low cost Housing Cheras	Malays	45.6	31.2

Table IV: Prevalence of Overweight and Obesity by ethnic group

	Overweight (%)			Obese (%)		
	Malays	Chinese	Indians	Malays	Chinese	Indians
NHMS II	16.5	15.1	18.6	5.1	3.5	5.0
MANS 2003	27.2	25.0	31.0	15.3	7.2	12.7
NSCVDRF 2004				13.6	8.5	13.5
NHMS III	29.8	28.5	33.2	16.6	8.7	17.7
NHMS 2011	31.1	27.6	30.8	18.7	9.7	20.6
NHMS 2015	31.0	28.1	35.0	21.1	11.7	27.1

Table V: Prevalence of Overweight and Obesity by sex and ethnic groups

	Overweight (%)						Obese (%)					
	Men			Women			Men			Women		
	Malays	Chinese	Indians	Malays	Chinese	Indians	Malays	Chinese	Indians	Malays	Chinese	Indians
NHMS 1996	20.0	24.5	24.2	23.9	18.7	25.6	4.5	4.7	3.8	9.5	5.3	9.8
MANS 2003	29.3	25.2	29.3	24.9	20.9	32.6	11.3	7.8	10.4	19.6	6.6	14.8
NSCVDRF 2004							10.5	8.4	9.8	16.6	8.5	17.2

Table VI: Prevalence of Overweight and Obesity by sex among *bumiputera* in Sabah and Sarawak

	Overweight				Obese			
	Men		Women		Men		Women	
	Bumiputra Sabah	Bumiputra Sarawak	Bumiputra Sabah	Bumiputra Sarawak	Bumiputra Sabah	Bumiputra Sarawak	Bumiputra Sabah	Bumiputra Sarawak
MANS 2003	24.3	24.6	23.2	31.9	8.4	5.3	7.4	8.4
NSCVDRF 2004					6.1	9.3	8.5	12.3

Table VII: The prevalence of overweight and obesity by state in Malaysia

	Overweight (%)				Obesity (%)			
	NHMS II	NMHS III	NHMS 2011	NHMS 2015	NHMS II	NMHS III	NHMS 2011	NMHS 2015
Johore	17.4	28.9	28.5	31.0	4.4	14.1	15.9	18.1
Kedah	14.9	31.1	31.6	30.1	3.3	15.5	15.2	20.5
Kelantan	12.9	28.3	31.5	30.3	3.4	12.5	16.2	16.2
Melaka	18.9	31.1	25.7	31.8	5.1	17.4	17.7	21.9
N Sembilan	19.4	29.5	27.6	27.7	6.3	18.6	16.0	23.5
Pahang	18.3	28.8	30.2	26.9	5.6	15.3	15.3	19.4
Penang	15.9	29.3	31.1	30.6	3.7	13.7	12.8	13.8
Perak	18.0	27.6	31.9	29.8	4.7	12.9	16.2	17.5
Perlis	18.2	32.1	29.5	30.2	5.1	17.2	21.7	22.3
Sabah	14.5	24.9	28.8	28.2	3.4	9.7	10.6	13.4
Sarawak	14.2	28.7	30.3	30.1	3.4	11.5	14.0	18.4
Selangor	17.0	31.0	27.3	30.3	4.8	16.0	17.1	18.7
Terengganu	17.9	28.6	32.8	28.9	5.8	15.2	14.0	18.6
Kuala Lumpur	17.5	29.8	29.2	33.7	4.8	12.5	13.5	14.9
Putrajaya				37.0				25.8

national sample.¹³ It has also been noted that being overweight and obese was associated with earlier menarche among women in a study of university students.¹⁶

Ethnic Differences

Across the national population surveys, **Indians are more overweight than Chinese and Malays.**^{6,8,9,10} (Table IV) The prevalence among Malays and Chinese appear to have stabilised, but among Indians the NHMS 2011 survey showed an unusual decrease followed by a steep rise in 2015. The obesity trend is clearer. Indians are becoming much more obese, with rates approaching three times more than Chinese.¹⁰

Indians of both sexes are more overweight than Chinese and Malays (Table V), the difference between Indian women and the other ethnic groups being wider than among the men.^{4,6,8} Data comparing men and women separately by ethnic groups are only available in three studies.^{4,6,7} Malay and Indian women were about equally obese in 2004 but Chinese women have only about half their prevalence rates. Chinese women are about equally as obese as Chinese men, but both Malay and Indian women are much more obese than their male counterparts. Among men, Chinese had the highest prevalence of obesity in 1996, but they have been overtaken by both Indian and Malay men in later studies.^{6,7,8}

Two studies listed the *bumiputera* of Sarawak and Sabah as separate categories^{6,7} which allows better observations to be made than when they are put together as just other indigenous people or others.^{4,8,9} The results shown in Table VI are inconsistent, probably due to sampling error as there are many *bumiputera* groups spread over a wide area in both

states. Their prevalence of overweight and obesity in 2003-2004 are lower than those of Indians and Malays and comparable to the rates among Chinese. It is hard to say with certainty whether the men or women are more overweight and obese. Except for one study which found *bumiputera* men in Sabah more overweight and obese than women (MANS), the rest of the data shows *bumiputera* women in Sarawak more overweight and obese than men, as did the NSCVDRF study find in contradiction with the MANS data (Table VI). Listed as other *bumiputera* in the NHMS 2011 and NHMS 2015, they have overweight rates similar to other races and obesity rates (14.1%, in 2011 and 18.0% in 2015) higher than Chinese but not as high as Malays and Indians.¹⁰

The ethnic group with the lowest prevalence of obesity in Malaysia are the Orang Asli. None of the Orang Asli were obese in the MANS study, and only 15% were overweight, but they only had a sample size of 28 Orang Asli. We must look at more focused studies for information. Chronic Energy Deficiency (CED) or under-nutrition (BMI < 18.5 kg/m²) has been and is still the larger nutritional problem among Orang Asli, but that is not the subject of this review.

A nutritional status survey of Orang Asli adults (Jahai, 58.7% Temiar, 41.3%) in Lembah Belu, Grik, of 138 subjects found 26.7% underweight and 10.1% were either overweight/obese.²⁵ Based on percentage body fat and waist circumference (WHO criteria) only 1 (0.7%) was obese. A study of 57 adult Orang Asli (Che Wong) in Pahang found 3 men (10.3%) and 8 women (29%) overweight and 1 man (3.3%) obese.²⁶ However, where the Orang Asli live very close to economic development such as in Sungai Rul in Cameron Highlands, among 138 respondents, by BMI 25.4%

Table VIII: Prevalence of Overweight and Obesity in several small localised studies

Author, year of study	Sample size	Age group (years)	Characteristics	Ethnicity (%)	Overweight	Obesity
Yunus 1999 ²⁹	570	>15	Hoseholds in Dengkil, Selangor	Malays=23.3 Chinese=57.1 Indians=30.5 Orang Asli=30.8		12.0 14.3 10.5 11.5
Hapizah ³⁰	609	30-65	Rural Community Raub, Pahang	Malays	33.5	11.2
Rampal 2004 ³¹	2219	>15	Households in Selangor	Malays=52.9 Chinese=30.9 Indians=15.4		15.2 7.3 11.6
Mohd Nazri 2005 ³²	348	>18	Households in Pulau Kundur, Kelantan	Malays=99.4	49.1	
Chang ³³	260	20-65	Rural Community, Serian, Sarawak	Malays=32.3 Bidayuh=33.1 Iban=34.6	39.6	14.3 11.6 10.0
Wan Nazaimoon 2007 ³⁴	4428	>18	Households in 5 Different states	Malays=62.5 Chinese=14.6 Indians=8.5 Ind Sabah=12.2	34.0 32.1 39.5 30.9	23.2 8.2 24.6 12.3
Akter 2007 ³⁵	219	>18	Bukit Sekelau (rural) Pahang	Malays	54.8(BMI>27.5)	
Narayan ³⁶	441	>20	Coastal Viages, Kedah	Malays	25.9	17.0
Suzana ¹²	820	>60	4 Rural Villages	Malays	24.7	11.4
Hamid Jan 2009 ³⁷	297	18-59	Bachok, Kelantan	Malays	41.7	13.4
Rampal 2010 ³⁸	454	30-68	University staff in Selangor	Malays=86.3 Chinese=8.8 Indians=4.9	30.1 37.5 36.4	12.0 17.5 0
Chew 2011 ³⁹	258	>21	Suburban New Village Selangor	Chinese	40	
Hazizi ⁴⁰	233	18-59	Government Employees Penang	Malays	29.6	20.6
Ayiesah ⁴¹	82	21-59	Military Hospital Staff Malacca	Malays	24.3	58.5
Ayiesah ⁴¹	211	19-24	Medical Students	Malays=63.5	16.6	3.8
Kabir, 2012-14 ⁴³	945	20-43	Postgraduate University Students,	Malays=79.3 Chinese=13.5 Indians=5.0 Others=2.2	23.1	8.9

Table IX: Physical Activity among Malaysians

	Adequate Exercise		Physically Inactive	
	Men	Women	Men	Women
NHMS II	16.2%	7.7%	60%	75%
MANS	18.9%	9.4%	60.0%	77.7%
MyNCDS-1			55.4%	60.1%
NMHS III			35.3%	50.5%
NMHS 2015			28.9%	38.3%

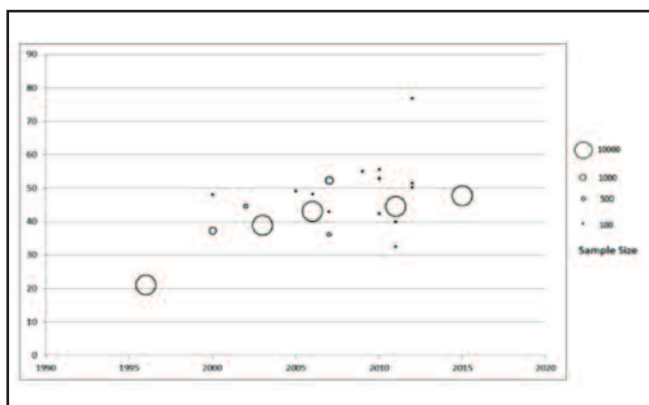


Fig. 1: Percentage of Malaysians overweight and obese (BMI>25kg/m²) in studies from 1996 to 2015.

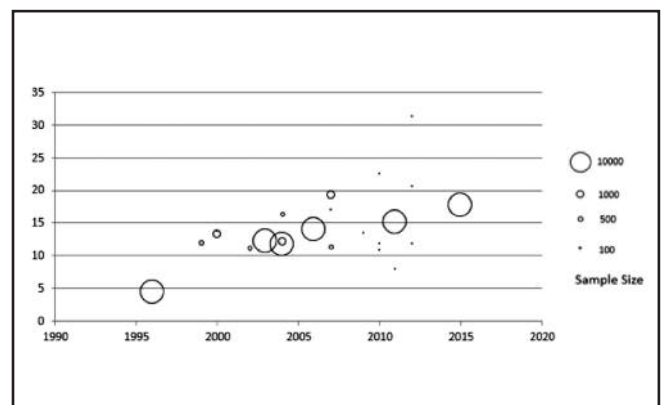


Fig. 2: Percentage of Malaysians obese (BMI>30kg/m²) in studies from 1996 to 2015.

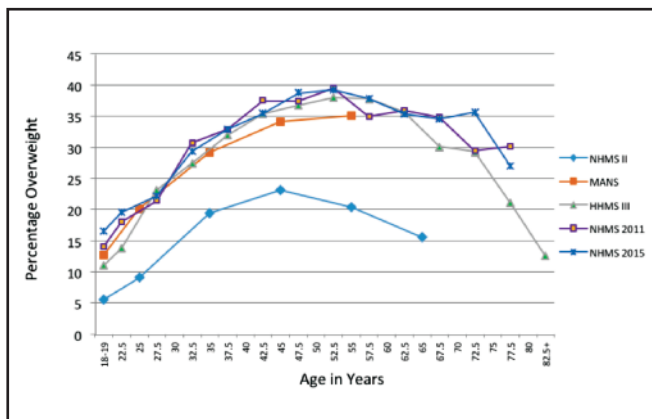


Fig. 3: Prevalence of Overweight (BMI 25-29kg/m²) among Malaysians of Different Age Groups.

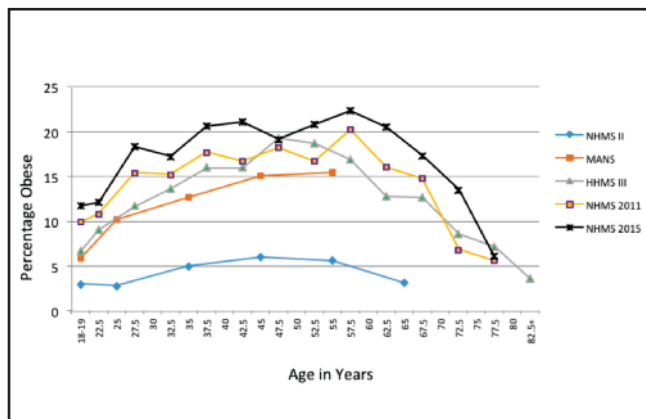


Fig. 4: Prevalence of Obesity (BMI >30kg/m²) among Malaysians of Different Age Groups.

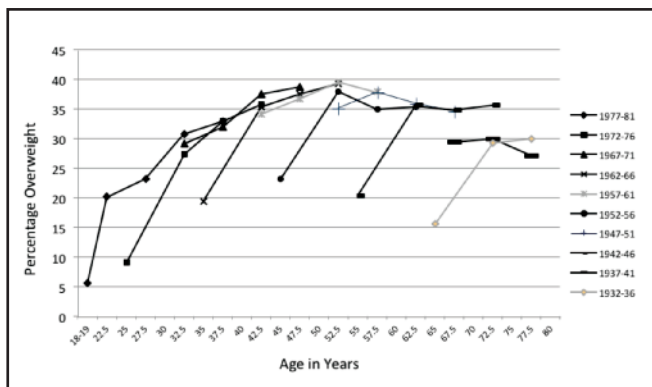


Fig. 5: Prevalence of Overweight at Various Age Groups for Different Birth Cohorts using data from NHMS II, MANS, NHMS III, NHMS 2011 and NHMS 2015.

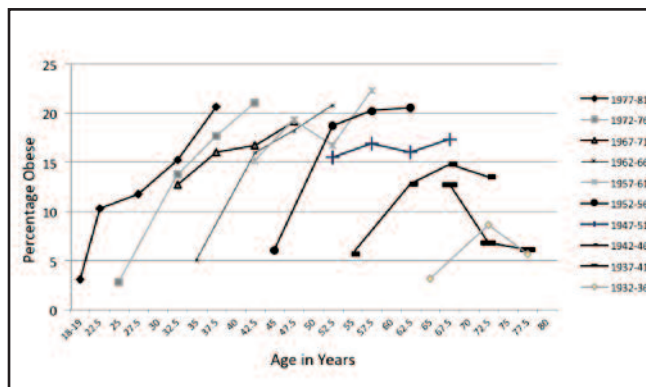


Fig. 6: Prevalence of Obesity (BMI >30kg/m²) at Various Age Groups for Different Birth Cohorts using data from NHMS II, MANS, NHMS III and NHMS 2011.

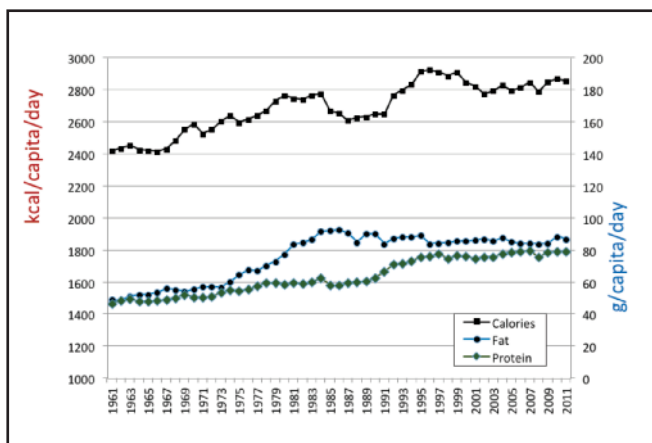


Fig. 7: Change in available calories, fat and protein per capita in Malaysia 1961-2011.

Source: FAO food balance sheet

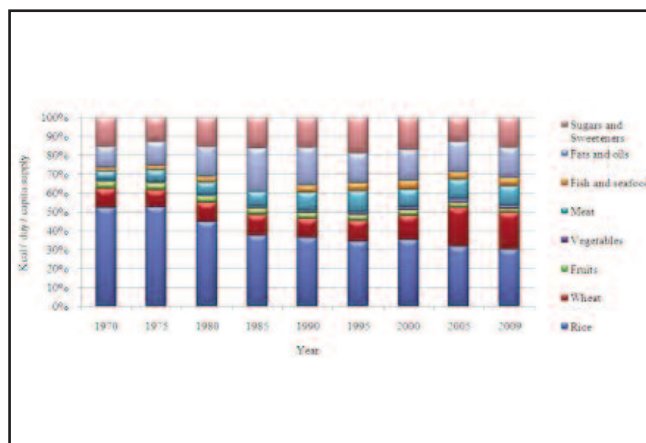


Fig. 8: Changes in source of calories in Malaysia between 1970 and 2009.

Source: Jan Mei Soon, E. Siong Tee. Changing Trends in Dietary Pattern and Implications to Food and Nutrition Security in Association of Southeast Asian Nations (ASEAN). International Journal of Nutrition and Food Sciences. Vol. 3, No. 4, 2014, pp. 259-269. doi: 10.11648/j.ijnfs.20140304.15

were overweight and 34.8% obese.²⁷ In wide survey (n=636) of Orang Asli, classifying them by tribes (Proto-Malays, Senois and Negritos), as well as by socio-economic groups (Urbanized City Fringe Dwellers (UCFD), Resettled Communities (UC) and Deep Forest Hunter Gatherers (DFHG), Phipps *et al.* found the prevalence of obesity ranged from 7.5-10.0% among the Proto-Malay, 4.5-10.0% among Senoi and only 2.6-5.5% among Negritos. By socio-economic groups, 31.6% of UCFD, 12.0% of RC and 2.0% of DFHG were obese.²⁸

Geographical Variations

Sabah, Sarawak, Kedah and Kelantan showed the lowest rates of overweight (12.9%-14.9%) and obesity (3.3%-3.4%) in the NHMS II in comparison to other states (overweight =15.9%-19.4%, obesity=3.7%-6.3%) (Table VII. Negeri Sembilan had the highest rates of overweight and obese adults.⁴ In the NHMS III only Sabah stood slightly apart with low rates of overweight (24.9%) and obesity (9.7%).⁸ The other states had rates of overweight between 27.6% (Perak) and 32.1% (Perlis) and rates of 11.5% (Sarawak) and 18.6% (Negeri Sembilan) for obesity. Sabah (10.6%) continued to show the lowest rate for obesity in the NMHS 2011, but Melaka had the lower prevalence of overweight (25.7%).⁹ The trend indicates that over these critical years nutritional availability, the main driver for obesity levelled out geographically throughout Malaysia. The latest NHMS 2015 showed that Putrajaya has the highest rates of obesity. Obesity is lowest in Penang and Kuala Lumpur, as well as Sabah, although the prevalence of overweight is similar to other states.¹⁰

The MANS study also looked at geographical variation and grouped the states in Peninsular Malaysia into four groups, Northern, Central, South and East, besides Sabah and Sarawak.⁶ This study considered the difference by sex which the NHMS II did not. There was no significant difference in the overweight category. Neither was there a significant difference in obesity among men. But women in Sabah (8.4%) and Sarawak (9.33%) were much less obese than in Peninsular Malaysia (12.5-13.8%). Women in the Southern Peninsular states had the highest prevalence of obesity (13.8%).

Most studies in the twenty-first century **has found no difference in the prevalence of overweight and obesity between rural and urban areas.**^{6,7,8,9,10}

Although large national studies provide a picture of the average and overall prevalence of obesity, the Malaysian population is not homogenous. Age, sex, locality and social characteristics produce variations in the prevalence of obesity. Several small localised studies have mapped out finding is certain pockets of the population. Table VIII shows the prevalence of obesity found in several of these studies.

Social and Economic Factors

Education

A common finding in the large nutritional status population studies is that those with tertiary education have slightly lower than those with primary and secondary education.^{4,6,8,9,10} However those with no education have the lowest overweight and obesity rates.

Occupation

The studies have not exhaustively nor consistently listed all occupations. However, one category that are **often most obese are the Administrative,⁴ or Senior Officer/Manager⁸** or as listed in the NMHS 2011; Government/Semi government employee.^{9,10} Although these terms are not equivalent, these categories have been the most obese or overweight in their respective studies. On the other hand, professionals are not usually most obese. Retirees were not an obese group before but are in 2015 group with high obesity.¹⁰ Private employees and those self-employed are less obese.^{9,10} The other occupation group that is also either most overweight or obese are **housewives.**^{8,9,10} Nazri *et al.*⁴⁴ and Lim *et al.*⁴⁵ report that shift work was associated with higher BMI among male and female factory workers. Moy *et al.* reported similar findings among mainly female medical care shift workers.⁴⁶

Income

The prevalence of obesity in Malaysia shows that food availability is to a large extent is no longer dependant on having enough income. There is a trend that the prevalence of overweight and obesity rises slowly from the poorest groups to the personal or household income level of RM4,000 a month.^{4,8,9} After that, the prevalence drops slightly at first, in the RM4,000-RM5,000 bracket and noticeably in the >RM5,000 bracket. In the NMHS II data the lowest income group (<RM400) did appear to have noticeably lower prevalence of overweight (24.9%) and obesity (11.5%) compared to a few brackets above (eg RM1,000-RM1,999 = 30% overweight, 15.4% obesity)⁴ but in the NMHS 2011, that poorest bracket (<RM400) have higher rates than the brackets above it.⁹ Tan AKG *et al.* however have contrary conclusions analysing data from the Malaysia Non-Communicable Disease Surveillance-1 (MyNCDS-1).⁴⁷ The NHMS 2015 records income <RM1,000 as the lowest bracket, and there is a slight rising trend with income up to the RM9,000-RM10,000 bracket. The with income above RM10,000 drop in obesity rates.¹⁰

In a study of low income rural households in Selangor, Zalilah and Khor found that more women from food insecure households (56.0%, 65/116) were overweight and obese compared to their food secure counterparts (40.5%, 34/84). Food secure women spent more time in economic activities while food insecure women spent more time in domestic and leisure activities. The hypothesis that food insecurity may lead to binge eating, needs further investigation.⁴⁸ Ihab *et al.* have also reported on the phenomenon of maternal obesity in the presence of childhood malnutrition in low income households. They found 52.0% (116/223) Malay women welfare recipients in Bachok, Kelantan were overweight/obese, while 61.0% (136/223) of the children were underweight. There were 66 pairs (29.6%) of overweight/obese mothers with underweight children. More than half (57%) were single female-headed households, 69% of mothers were employed. Divorced or widowed poor women were five times more likely to be associated with the dual malnutrition condition than poor married women. Large households and a shift to higher consumption of refined grains, meat and edible oils inadequate in micronutrients (nutrition transition) may also be factors underlying this situation.⁴⁹

Dunn *et. al.* have analysed the relationship between socioeconomic characteristics and BMI between Malays and Chinese by quintile regression and concluded that reduction of economic inequality is unlikely to eliminate obesity disparities between Malays and Chinese.⁵⁰ Increased effort to alter lifestyle behaviour, they believe, are required.

Abdominal Obesity(AO) and other measures of obesity

There has been debate as a result of some evidence that although BMI is easily measured, it is not a good predictor of cardiovascular and obesity related health risks. Waist circumference(WC), a proxy measure of body fat is said to be a better predictor.⁵¹ BMI is even a poorer predictor of body fat in Asian ethnic groups when calculations derived from a Caucasian population is used. There is concern that among Asians the risk of diabetes and other chronic diseases starts to increase even when BMI or waist circumference are well within the accepted range for Europeans⁵² and it has been suggested that in Asians, the BMI cut-offs should be 23.0kg/m² for overweight and 27.0 kg/m² for obese, lower than the WHO criteria.^{53,54,55}

Investigating Cut-off Values

Asians are thought to be more prone to central or visceral obesity (AO). Studies have therefore been done to find more suitable parameters for obesity and its relationship to cardiovascular disease, dyslipidaemia, hypertension and diabetes among Asians^{56,57} and it has been replicated in Malaysia.^{58,59} Using Receiver Operating Characteristic(ROC) analysis to compare the predictive validity and optimal cut-off values, and the Area under the curve (AUC) to determine its diagnostic power, Zaki *et. al.* found the optimal cut-off value for WC varied from 83-92 cm in men and from 83-88cm in women in Malaysia, in a sample size of 1,893 individuals from 93 primary care clinics.⁵⁸ They also found the optimal BMI cut-off values predicting dyslipidaemia, hypertension, diabetes mellitus or at least one CVD risk factor varied from 23.5-25.5 kg/m² in men and 24.9-27.4 kg/m² in women. They concluded that WC may be a better indicator for predicting obesity related CVD risk. BMI is also a weak predictor for diabetes and WC appeared to be better. They also found that at a cut-off for WC>90 cm for men and >80 cm for women, AO was present in approximately 71% patients with lipid disorder, in 76% with hypertension and in 75% with diabetes.⁶⁰ Aye and Malek also noted WC was a better predictor than BMI of metabolic risk factors for developing going by the IDF definition of Metabolic Syndrome.⁵⁹ The optimal cut-off point of WC they found to predict individual metabolic risk was 84.5–91.0 cm in females and 86.5–91.0 cm for males.

In Caucasian populations the recommended cut-off points for waist circumference are, Waist Action Level 1 (overweight): ≥ 94 cm for men and ≥ 80 cm for women; and Waist Action Level 2 (obese) ≥ 102 cm for men and ≥ 88 cm for women. Using data from 32,773 subjects who participated in the NHMS III, Kee *et. al.* found that the ROC analyses showed that the appropriate screening cut-off points for WC to identify overweight subjects with BMI ≥ 25 kg/m² was 86.0 cm for men (sensitivity=83.6%, specificity=82.5%), and 79.1 cm for women (sensitivity=85.0%, specificity=79.5%). The cut-off points to identify obese subjects with BMI ≥ 30 kg/m²

was 93.2 cm for men (sensitivity=86.5%, specificity=85.7%) and 85.2 cm for women (sensitivity=77.9%, specificity=78.0%).⁶¹

Prevalence of AO

Using standard WC cut-offs of >102 cm in men, >88 cm in women (WHO 1998) Kee *et.al.* found the overall national prevalence of AO among Malaysian adults in the NHMS III was 17.4%.⁶² The prevalence was much higher in women (26.0%) than in men (7.2%) (OR: 4.2). The prevalence of AO increased steadily with age until the age of 50 to 59 years, after which the prevalence declined. The prevalence was higher among the Indians (OR: 3.0) and Malays (OR: 1.8) compared to others. With regard to marital status, respondents who were ever married had the higher risk of AO compared to not married (OR: 1.4). As with obesity measured by BMI, an inverse relationship was observed between the level of education and prevalence of AO. Respondents who received no formal education had the highest prevalence at 23.7%, followed by those with primary education (21.2%), secondary education (15.2%) and tertiary education (12.1%). By occupational status, housewives had the highest prevalence of AO compared to other occupations (OR: 1.4, 95% CI: 1.1, 1.7). Among the household income categories, prevalence of AO was lowest in households with greater than RM5000(13.7%) Income groups between RM1000-3000 had highest rates (18.2-18.4%). The prevalence of abdominal obesity among the elderly (≥ 60 years) in the NHMS III in 2006 was 21.4%, 33.4% for women and 7.4% for men.¹¹

The prevalence of abdominal obesity by the same criteria rose to 23% in NHMS 2015, with a similar pattern if differences between groups.¹⁰ Using the WC cut-off of >90cm in men and >80cm in women, the prevalence of AO was 48.6%.

A normal BMI may hide individuals with health risks due to excess fat present as AO. Norafidah *et. al.* noted that being female and non-Malay were factors that were found to be associated with abdominal obesity in the normal BMI population.⁶³

Body Fat Percentage

In a study excluding underweight individuals, Goonasegaran *et. al.* put forward the case that body fat percentage (BFP) measuring neck, waist and hip circumference and using the US Navy formula, was a superior measure of obesity to BMI better at differentiating between lean mass and adipose tissue in those mildly obese or overweight.⁶⁴

Morbid Obesity

Obesity is recognised as a risk factor, increasing an individual's chance of having several major diseases. However, marked obesity of a BMI >40kg/m² is commonly termed morbid obesity, and a disease in its own right. In 1996, 0.3% of the population were found to have a BMI of greater than 40.0kg/m². Women (0.4%) had a high rate than men (0.2%). Malay women (0.6%) had the highest prevalence of super obesity.⁴ Data from the NMHSIII showed the overall prevalence of morbid obesity had increased to 1.0%.⁸ The peak age of morbid obesity was 45-49 years (1.3%). Indians(1.6%) were the ethnic groups with the

highest rate, and housewives (1.5%) the occupation group most morbidly obese. By 2011 the overall prevalence of morbid obesity had risen to 1.3%. Females (1.7%) continued to outnumber males (1.0%).⁹ Indians (2.7%) continued to be most affected, followed by Malays (1.9%) but Chinese (0.3%) appeared to be significantly less affected. In NHMS 2015 the rate of morbid obesity crept up to 1.4%, and the peak age was seen among the 30-34 years group (2.2%).¹⁰ Further comment may be unreliable because the counted numbers are small.

RISK FACTORS

Obesity develops when energy intake exceeds expenditure. While recognizing that genetic factors and human metabolism can modify the development of obesity, it is obvious that the two greatest driving forces for the rising prevalence of obesity in Malaysia today are the increase of food availability and resulting food consumption linked with inadequate physical activity.

The end of the twentieth century saw economic development in Malaysia that made food easily available. The per capita gross national product of Malaysia grew an average of 8% per annum between 1980-2000.⁶⁵ Urbanisation rose from 25% in 1969 to 41% in 1990 and is expected to reach 60% by 2020.⁶⁶ Poverty rates fell. The opportunity to become overweight opened up for many.

Food Intake

The quantity and type of food available in Malaysia over the last several decades allow us to understand the rise in prevalence of obesity in the population. Total availability of calories per capita per day in Malaysia was estimated at 2430 kcal in 1961 and increased to 2923 - 2990 kcal in 2007, a 20% increase over 40 years.^{67,68} Although food availability actually fluctuates from year to year, Davey *et al.* point out that in no year after 1992 was there less than 2780 kcal available per capita per day.⁶⁹ The FOA food balance sheet shows that available food calories has not continued to rise the last 10 years (Figure 7). Rising prosperity meant the proportion of household income spent on food and non-alcoholic beverages declined from 23.8% in 1992-4 to 20.3% in 2009-10, even though in absolute terms the amount spent was RM1161 in 1992-4 compared to RM2190 in 2009-10.⁶⁶

Calories available from animal products per capita per day rose from 267 kcal in 1967 to 485 kcal in 2007, a rise of 82%, but Figure 7 shows that according to FAO food balance sheet the amount of fats and protein available per capita has also remained stable. The amount of available sugar and sweeteners per capita per year rose from 28.8 kg to 48.7 kg between 1967 and 2007, a rise of 70%. On the other hand the proportion of calories obtained from cereals decreased from 61% to 41% (Figure 8). For a long time while the price of sugar rose in the world market, its price to the consumer in Malaysia was kept low by a hefty subsidy from the government which was only removed in the year 2014.⁷⁰ Given there exists some inequality of distribution, the abundance of food explains why almost any segment of the population can become obese.

Data about what the actual energy intake of individuals are is less clear. The mean calorie intake in poor villages, in the

1980s and 1990s, was noted to be 1870 kcal per person per day.⁷¹ A 3-day food record survey of 409 adults with normal BMI across Malaysia in 1992-3 recorded a mean energy intake of 2163 kcal/day among the men and 1718 kcal/day among women respectively.⁷² Overall, 14% of the total energy was derived from protein, 23% from fat and 63% from carbohydrate, but urbanites consumed a higher proportion of energy in fats (29%) compared to rural subjects (20%). The energy intake of Indians, surprisingly, was significantly lower than that of other ethnic groups. Malay women recorded a significantly higher energy intake than other ethnic groups. Urban male subjects consumed significantly more energy (2275 kcal) than their rural counterparts (2024 kcal), but this was not the case in women. In both men and women, fat intake was significantly higher in Chinese and urban subjects.⁷² Among three similar studies of urban post-menopausal Malay and Chinese women, the investigators reported similar energy distribution of their subjects' dietary intake, which consisted of 53-55% carbohydrate, 15-17% protein and 29-30% fat. Malay women reported a higher daily calorie intake (mean values 1649-1747 kcal) compared to Chinese women (mean values 1550-1591 kcal).^{73,74,75}

Among Malay women Employee Provident Fund (EPF) office workers in Kuala Lumpur and Selangor, Lee *et al.* found that the mean energy intake for normal weight, overweight and obese subjects was 1685±199 kcal/day, 1810±166 kcal/day and 2119±222 kcal/day, respectively.²¹ Evidence that the economic transformation of Malaysia from a rural agrarian economy to an urban commercial society has impacted dietary habits can be seen in a dietary survey of selected women electronic factory workers by Lim *et al.* in 2000. Even though it was only a selected/invited sample of 122 women, of whom one third each was normal/underweight, overweight and obese, it revealed that such women tended to eat meals at irregular hours (61.5%) and nearly half thought healthy foods did not taste nice (47.5%) or were expensive (45.1%). They had a high frequency of taking foods high in fat content and of a diet lacking in variety. Living in a hostel, surprisingly, was a factor associated with less risk of obesity, but the similarity of frequency of pattern of food consumption led the investigators to believe they shared the risk of being obese in the future. Exercise, even when reported, did not reach an intensity to be of benefit. Only 39.3% reported ever trying to lose weight. However, their preference was for slimming products rather than a healthier lifestyle or dietary changes.⁴⁵

Suriani *et al.* surveyed overweight and obese working women regards barriers they faced controlling food intake. As regards not eating healthily more frequently the commonest reasons were 'lack of knowledge' (79.3%), followed by 'lack of motivation' (72.1%) and 'family commitment' (71.4%). As regards controlling the quantity of food the commonest responses were 'attend meetings often' (60.0%), followed by 'difficult when eating out' (57.9%).⁷⁶

Secondary analysis of the NHMS III food label study of 4,565 obese respondents found they claimed to read and understand the food label. 74.5% read the expiry date but less than 20% read information about food component content.⁷⁷

The consumption of soft drinks was reported to be a significant risk factor that is associated with being overweight among medical student.⁷⁸ Choong *et al.* found no correlation between preference for and frequency of consumption of salty food and being overweight among 300 university students.⁷⁹ Swarna Nantha argues that the increasing rate of sugar consumption in Malaysia should be viewed as sugar addiction and addictive behavior considered in relation to health policy development regarding obesity.⁸⁰

Physical Activity

The NMHS surveys, and other large surveys like the MANS, and MyNCDS-1 have reported physical activity data of Malaysian adults, and have wide ranging values (Table IX). However the trend appears that fewer people are currently inactive. It would go beyond the scope of this review to report these findings in depth and review all studies on physical activity.

Poh *et al.* examined the physical activity status of 7,349 respondents of the MANS study of 2003, which covered all states and ethnic groups in Malaysia.⁸¹

Transport: In that study, 74.4% used passive modes of transport such as cars and motorcycles as their main mode of transport. 9.2% used public transport, (which involves slightly more physical activity) and 17.7% walked or cycled. Not surprisingly the rural population walked more (23% vs 14% urban). The bumiputra of Sabah, Sarawak and Orang Asli walked much more (45-50%) than the Malays, Chinese and Indians (11-15%). More women (24.3%) walked than men (13.8%).⁸¹

Exercise: Poh *et al.* found that 31.3% of the population had engaged in some form of exercise in the two weeks prior to the interview (ever-exercised) (40.0% of men, 22.3% of women). 14.2% of the respondents reported adequate exercise, defined as at least 20 minute sessions at least three times a week. In both these measures of exercise the rate was higher in urban compared to rural adults. The East Coast states had an unusually low rates of exercise among the different regions. Young adults (18-19years) reported the highest rates of exercise. The overweight group reported most exercise, even exceeding the normal and underweight. The obese exercised least.⁸¹

Physical Activity Pattern: Physical activity level (PAL) was calculated as the ratio of total energy expenditure (TEE) to basal metabolic rate(BMR). Across the population the PAL was 1.6-1.7 and did not differ much between urban or rural areas, between men and women, between ethnic groups, or between normal or overweight group.⁸¹ The desirable PAL score to avoid obesity is one above 1.75. A low score reflecting a very sedentary lifestyle is 1.4.

The WHO study on non-communicable disease risk factors and socioeconomic inequalities found that men in rural area were more likely to be engaged in occupations with a high level of physical activity (33.7%) compared to urban dwellers (23.5%), similarly for women (19.7% rural vs 15.9% urban). The lower income men (<RM1000) also had a higher level of occupational physical activity (31.2%) compared to high

income earners (>RM3999) (22.2%) and the same was true for women (16.4% high income vs 12.1% low income). On the other hand higher education and higher income was associated with more leisure time physical activity for both men and women. Indian men had an unusually low rate of leisure time physical activity.⁸²

Kabir *et al.* surveyed 945 post-graduate students in University Putra Malaysia(UPM), with a mean age of 27 years and found 32% had a BMI >25kg/m². 44% had low physical activity and they were twice as likely to be overweight or obese.⁴¹

A study of 136 security guards and their wives in Kuala Lumpur found that only 39.2% ever-exercised and 13.8% exercised adequately.⁸³ Hazizi *et al.* determined that among 210 Malay employees in the Federal Government Building in Penang that 64.8% had low physical activity, measured by an accelerometer clipped to the subjects belt/skirt/trousers at the waist.⁴⁰

Among women working in corporate companies in Petaling Jaya, aged between 18-55 years, 48.8% were found to be moderately active and 28.8% were highly active according to the International Physical Activity Questionnaire-short form (IPAQ,2005) in a study by Siti Affira *et al.* These rates were higher than in larger population surveys and they found monthly income correlated positively with physical activity. There was however no significant association between job category and physical activity.²² Lim *et al.* found that 29.5% of women working in electronic factories in Selangor had adequate exercise.⁴⁵

Wan Nudri *et al.* found that men who reported having no exercise were significantly more overweight than men who regularly exercised and sportsmen who actively participated in competition, in a cross-sectional study of randomly selected men from government departments in Kota Bharu.⁸⁴ Low physical activity also correlated to obesity in studies among staff in a military hospital and individuals attending health clinics in Sepang, by Ayiesah *et al.*⁴¹ and Hejar AR *et al.*⁸⁵ respectively, and also in government employees in Penang.⁴⁰

Among the obese pre-diabetics in Negeri Sembilan, Norliza et al. found 60.8% were physically inactive using the IPAQ,2005.⁸⁶

ASSOCIATION OF OBESITY WITH OTHER DISEASES

Metabolic Syndrome

Central obesity, raised blood lipids, hypertension and a raised fasting blood sugar have been collectively recognised as manifestation of an insulin resistant state. The prevalence of metabolic syndrome has been addressed in a separate article.⁸⁷ This section will only highlight the various elements of metabolic syndrome as they are related to obesity. In any population of obese individuals, each of these other factors can be expected to be high.

For example, Mafauzy reported in a study of 1,099 diabetic clinic patients across 19 public hospitals (Ministry of Health

and University Hospitals) in Peninsular Malaysia) that 66.9% of males and 82.1% of females had a waist circumference (Asian WC) >90cm(males) and >80cm(females).⁸⁸ Abougambou *et al.* found that 81.5% of their patients at the diabetic outpatient clinics from Hospital Universiti Sains Malaysia were obese.⁸⁹ 66.8% of diabetics were found overweight and 15.8% obese in a study of 196 type 2 diabetic patients the Universiti Malaya Medical Centre primary health clinic.⁹⁰ Eid *et al.* noted that a BMI value above target level was observed in 66% (140/211) of their diabetic patients.⁹¹ Foo *et al.* found that 75%(121/161) of their diabetic subjects were centrally obese using the Asian WC criteria.⁹² They showed a predominance of insulin resistance over secretory dysfunction using the Homeostatic Model Assessment (HOMA) proposed by Matthews *et al.*⁹³ Lim *et al.* have confirmed a bimodal peak of blood glucose distribution with BMI in all ethnic groups in Malaysia.⁹⁴

Among 268 semi-urban pre-diabetics (individuals with blood glucose concentrations higher than normal but not high enough to be classified as diabetic) attending two primary care clinics, Norliza *et al.* found 21.6% were overweight and 71.3% obese. Using a health-related quality of life (HRQOL) survey they found those overweight and obese had a lower HRQOL score compared to the small number (7.1%) of normal weight individuals.⁸⁶

Hypertension has been noted to be more prevalence among the obese in numerous studies in Malaysia as well.^{95,96,97,98,99} even in rural Kedah³⁶ and Sarawak.³³ The same higher prevalence of raised blood cholesterol among the overweight and obese.^{33,36,39,95,96}

Cardiovascular Diseases

Su *et al.* found that although obesity as measured by BMI did not correlate to cardiovascular risks ($r=0.038$ $p=0.26$), as measured by the Framingham Risk Score (FRS), among urban Malaysians ($n=882$), other measures of obesity; namely waist-hip ratio(WHR) ($r=0.44$ $p<0.001$) waist circumference (WC) ($r=0.28$ $p<0.001$) and Waist to Height Ratio(WHtR) ($r=0.23$ $p<0.001$) were correlated to cardiovascular risks.¹⁰⁰ Moy *et al.* noted a weak but significant correlation between the FRS for coronary heart disease and three measure of obesity (BMI, WC and Weight-Height-Ratio) among Malay men working as security guards.¹⁰¹

In a cross-sectional study of 36 lean and 36 obese subjects, Al-Tahami *et al.* found that endothelial dependent vasodilatation was lower in obese compared to lean subjects (40.53 ± 6.59 vs 71.03 ± 7.13 AU).¹⁰² They also found lower adiponectin levels (8.80 ± 0.43 vs 25.93 ± 0.40 $\mu\text{g/ml}$) in obese compared to lean subjects. Sanip *et al.* found serum adiponectin levels positively correlated with the HOMA insulin sensitivity index but no correlation with microvascular endothelial function indices in a sample of 91 overweight and obese females with no other metabolic syndrome markers.¹⁰³ Nafikudin *et al.* found that the intima-media thickness of common carotid arteries measured by ultrasound were thicker among subjects with some obesity indices, especially those with familial hypercholesterolemia.¹⁰⁴

Surgeons at Hospital Universiti Sains Malaysia, Kubang Kerian reported that there was no significant difference in the surgical outcome of isolated coronary artery bypass graft between overweight and normal weight individuals in a study of 141 of their patients between 2001 and 2004.¹⁰⁵

Psychiatric Disorders

Norelrawati *et al.* found that among their schizophrenic patients attending follow-up at clinic 32% (69/216) were overweight and 28% (60/216) were obese. Again women were more obese than men. No particular type of antipsychotic agent was associated with a higher prevalence of obesity.¹⁰⁶ Ainsah *et al.* found 74.2% (72/97) of their patients on antipsychotics were overweight or obese (by Asian classification of overweight >23 kg/m^2), 71.4%(45/63) of those on atypical antipsychotics and 79.4%(27/34) of those on conventional antipsychotics. The mean WC of those on conventional antipsychotics (93.4cm) was significantly higher than for those on atypical antipsychotics (88.2cm). Those receiving a combination of depot antipsychotics also had a significantly higher WC than those who did not. However, being on concomitant antidepressants was not associated with any significant difference.¹⁰⁷ Binge eating disorder was not significantly higher among overweight and obese patients with schizophrenia compared to normal weight schizophrenics, in a study of 97 patients.¹⁰⁸ There was no significant difference in dietary intake and exercise scores between overweight and non-overweight schizophrenics either.

Reversing the view, Loo *et al.* surveyed 102 overweight or obese (BMI>23 kg/m^2) patients referred for dietary advice to a dietician clinic and found using the 30 question General Health Questionnaire that 15.7% had psychiatric illness.¹⁰⁹ Abdollahi and Mansor also showed that obese individuals with sedentary behaviour and poor body esteem were more likely to show social anxiety.¹¹⁰

A study on whether stress and depression had a causal link to abdominal obesity across 17 countries, in which Malaysia was included, found that stress and depression had no independent effect on abdominal obesity.¹¹¹

Night eating syndrome (NES) describes a condition characterized by morning anorexia, evening hyperphagia and insomnia. Nocturnal food ingestion is >50% of daily calories intake and occurs at least three times a week for a period of 3 months. Ainsah and Osman reported the case of a 65 year old Malay widower, whose wife and son had earlier left him; a retired army sergeant, with multiple medical problems and was chronically feeling depressed. He was morbidly obese with a BMI of 45 kg/m^2 and had problems with excessive weight gain since the age of 41years. He responded to diet and behaviour therapy and reduced his weight from 123 kg to 91 kg over 18 months.¹¹²

Pregnancy Induced Hypertension

In a small case-control study of 30 cases attending antenatal clinic matched with controls in the three selected health centres in Alor Gajah, Melaka, Adinegara and Razzak found that pregnancy induced hypertension(PIH) was significantly associated with obesity and being a housewife. However there

was no association at all between consumption of the varied food items and the development of PIH.¹¹³

Spontaneous Cerebrospinal Fluid Rhinorrhoea

Gendeh and Salina reported clinical data of eight patients diagnosed with spontaneous cerebrospinal fluid rhinorrhoea who had been treated at their tertiary referral centre between 1998 and 2007 and noted all of them were overweight (mean BMI 32.5 kg/m²) 7 out of the 8 were female. Central obesity raises intra-abdominal and intrathoracic pressure, increasing the cardiac-filling pressure which in turn impedes the venous return from the brain leading to raised intracranial pressure. Obese patients are also more prone to exaggerated oscillations in intracranial pressure and therefore more at risk of developing a CSF leak.¹¹⁴

Breast Cancer

Three studies have examined the nutritional status of breast cancer patients.^{19,20,23} Norsa'adah *et al.* noted that 48% of their women with breast cancer in Kelantan were overweight/obese and they thought that the rate was higher than the general population, compared to the NHMS II data.¹⁹ However, in view of the general rise in prevalence of obesity of that period around the year 2000, that may not be true.

A case control study of breast cancer patients in Kuala Lumpur matched for their age and menopausal status with volunteers at the National Cancer Society in 2006 found that 71% of breast cancer patients had a waist circumference >80cm compared to 40% among controls. Premenopausal breast cancer patients were four times more likely to have abdominal obesity.¹¹⁵

Yong found that in the year preceding diagnosis of breast cancer women on average lost weight (mean loss=0.7 kg).²⁰ However after diagnosis till the time of study these women had a mean gain in weight of 3.5 kg. Less than 20% of women actually lost weight with their encounter with breast cancer. Excluding those who lose weight on account of advanced breast cancer, women tend to over compensate nutritionally in the course of having breast cancer. Lua *et al.* found that 70% of their breast cancer patients were meeting more than their individual daily energy requirements.²³ However, only 31.7% achieved the recommended daily intake of fruits and vegetable.

Colorectal Cancer

Metabolic syndrome, of which obesity is a factor is a known risk factor for colorectal cancer and affirmed in Malaysia.¹¹⁶ It has also been suggested that obesity is a risk factor for colorectal adenoma. In a case-control study of 59 patients with colorectal adenomas matched with controls, waist circumference was the only factor that was found to significantly increase the risk for colorectal adenoma, and only in women. A waist circumference of >88 cm carried a 6 fold increased risk of having an adenoma.¹¹⁷

Chronic Periodontitis

Obesity has been identified as a risk factor of chronic periodontitis(CP). A study using convenience sampling of 165 participants from various clinics in Universiti Malaya Medical Centre, above 30years old and with a BMI

>27.5kg/m² found that 73.9% had CP, 55% of them moderate or severe CP.¹¹⁸

MANAGING OBESITY

Recognising the seriousness and magnitude of the growing problem of obesity, Clinical Guideline for the Management of Obesity were drawn up together and published by the Ministry of Health, the Academy of Medicine and several specialist medical societies under the chairmanship of Ikram SI in 2004. In addition to defining the problem, the document recommended strategies for weight loss. It outlined dietary therapy as well as physical therapy. It discussed the role of pharmacotherapy and surgery. It also acknowledges the role of counselling and behaviour therapy.¹¹⁹ The Malaysian Association for the Study of Obesity in Malaysia also produced a document on strategies to prevent obesity in 2005 under the chairmanship of Mohd Ismail N. Besides elucidating the role of diet and physical activity, the report recognised that managing obesity was a shared responsibility involving government, industry, professional bodies, non-governmental organisations, communities and individuals. It proposed that a National Steering Committee for the Prevention of Obesity be established. It recommended that working groups be formed in communities, schools, health care facilities and workplaces to educate the population and take action.¹²⁰

Behavioural Factors

Poh *et al.* found that working women in Kuala Lumpur were fairly knowledgeable concerning healthy body weight management. They found no difference between the normal weight and overweight women. School teachers were significantly more knowledgeable than civil servants in weight management matters. More overweight women (20%) had high knowledge level scores (75%) compared to normal weight women (15%).¹²¹

The management of obesity is intricately intertwined with behavioural change. Besides a minor role for medication and surgery, the mainstay of weight reduction is modification of dietary intake and physical activity. In a study of native Sarawakians living in villages who were overweight or obese, Chang found that 76.8% perceived that they were overweight/obese. As regards behaviour change, 60.5% (164/271) were in the pre-contemplation stage, which means they were not even thinking of behaviour change. The commonly used Transtheoretical Model of change (TTM), views change as a process that involves five stages. Pre-contemplation is the first stage. Contemplation is the second stage, where an individual is considering change within the next six months. 20.7% (56/271) of the overweight native Sarawakian villagers were in that stage. The remaining 18.9% (51/271) were in either the preparation stage (intending to take action within 30 days), the action stage (overt modification of behaviour of less than six months duration) or maintenance phase (behaviour change longer than six months). A higher level of education was the only factor that correlated with a higher level of preparedness for behavioural change.¹²² On the other hand, in a survey of university staff across the spectrum of weight distribution, done as a baseline for behaviour intervention, Ang *et al.* found that 50.7% (172/339) were in the preparation stage for

change; 30.0% (101/337) were either in the action or maintenance stage of change, 14.5% (49/337) were in the contemplation stage and only 5.0% (17/337) were in pre-contemplation.¹²³

Intervention Programmes

Moy *et al.* conducted an intervention programme involving Malay male security guards working in a public university in Kuala Lumpur, of whom 34% were overweight. The group received intensive individual and group counselling on diet, physical activity and quitting smoking, but they found at the end of 2 years there was no change in the BMI of the group.¹²⁴ Ramli *et al.* reported a six-month-long obesity health programme/study, which consisted of two weekly unsupervised exercise sessions and monthly dietary/health education sessions, conducted among overweight civil servants during office hours. Unfortunately there was no significant change in body weight, although the subject did show some improvement in indices of physical fitness.¹²⁵

Al-Qalah *et al.* surveyed 639 Malaysian working women in Putrajaya and Bangi to identify those who had successfully lost weight. Successful weight loss was defined as losing at least 10% of their highest lifetime body weight. They found 18.8% (120/639) experienced successful weight loss. The commonest dietary weight loss strategy used was to eat more fruits and vegetables (50.8%), followed by reducing the amount of food eaten (49.2%) and reducing fatty food intake (42.5%).¹²⁶

A total of 28 obese (BMI >30kg/m²) subjects at Obesity Clinic, Hospital Universiti Sains Malaysia, Kelantan completed a 12 week weight loss program consisting of dietary and exercise interventions. There was a significant mean weight change from 89.27 ± 2.78 kg to 83.11 ± 2.42 kg. Four subjects (14.3%) lost more than 10% of their body weight. There was also a significant reduction of waist circumference, BMI and fat-free mass. The investigators also found a significant decline in the levels of plasminogen activator inhibitor (PAI-1), plasminogen activator (t-PA) levels, thrombin activatable fibrinolytic inhibitor (TAFI) and fibrinogen alongside the weight reduction. They noted a significant correlation between BMI with fibrinogen and all three fibrinolytic markers suggesting a beneficial effect of this program on the hemostatic burden particularly on the fibrinolytic biomarkers.¹²⁷

Suriani *et al.* investigated two dietary control programmes for overweight and obese women in Putrajaya and Seremban. The first was a standard programme promoting food quantity control based on the national dietary guidelines. The faith-based programme, in addition contained relevant Islamic information to motivate participants. 84 Malay Muslim women chose the former and 56 chose the latter. The programme began with Ramadan and continued for three months after Ramadan. At that point in time, the mean BMI reduction in the standard dietary intervention was 0.16kg/m² (from 31.14 ± 4.26 kg/m² to 30.98 ± 4.28 kg/m²; P = 0.16; CI: -0.06–0.38) while it was 0.49kg/m² in the faith-based dietary intervention group (from 31.01 ± 4.07 kg/m² to 30.52 ± 4.03 kg/m²; P ≤ 0.01; CI: 0.22–0.75). 128,129,130

Teng *et al.* investigated the weight reduction effects of caloric restriction combined with two days a week of Muslim Sunnah fasting in a 12 week trial, among Malay men who had BMI between 23.0–29.0 kg/m². The 28 men in the intervention group, who were provided food guidelines, log books and contacted once a week, reduced caloric intake from a mean of 1707kcal by about 300kcal and lost an average of 2.8 kg. The control group on the other hand saw their mean intake increase slightly from 1755 kcal by about 60 kcal. DNA damaged, assessed by the alkaline comet assay and fluorescence microscopy decreased significantly in the intervention group, as did oxidative stress measured by plasma malondialdehyde.¹³¹

In a small study of 25 obese patient, Christopher *et al.* noted that a period of supervised regular exercise improved pulmonary function of obese patients and independent of the amount of weight loss.¹³²

The Malaysian Health Promotion Board funds projects run by non-governmental organisations, such as Kominuti Sihat Perkasa Negara (KOSPEN), Healthy Eating Campaigns, Nutrition Month campaigns. Ruzita *et al.* evaluated the effectiveness of 22 such projects on obesity conducted in the year 2010 by examining their final reports. 18 projects were of less than 3 months duration and 4 longer than 3 months. They judged 21 project to be of moderate quality and one of poor quality base on their achievement in health literacy.¹³³ In a study of 56 university employees assigned to either a 12 week programme of physical activity and dietary intervention or a control group, Soon *et al.* found no significant difference in obesity indices. In fact, although the lipid profile improved slightly in the intervention group, their weight and hip circumference increased.¹³⁴

In previous times and cultures being 'plump' or 'chubby' may have been perceived positively. However as in most cultures today, being obese is perceived negatively in Malaysia.¹³⁵ Action for weight loss is popular among the general population, even among the normal weight, and not only the obese. 37.7% of 1032 people surveyed in shopping centres in Kuala Lumpur admitted they have taken such action before. Only 32.6% of them were actually overweight or obese. 50.4% of those who have attempted to lose weight mistakenly perceived their weight category. The normal and underweight tend to be lower in weight than they imagined, while the overweight and obese tended to be heavier than they perceived. Dieting (89.5%) and exercise (81%) were the most popular weight loss measures, followed by slimming teas (24.9%), vitamins (21.9%) and chitosan(19.0%).¹³⁶

Pharmaceutical Agents

Suraya and Azmawati found that 41.6% (62/149) of overweight and obese (149/258) university students surveyed used non-prescription substances for weight loss management.¹³⁷

Liraglutide an analogue of Glucagon-like peptide-1 (GLP-1), stimulates insulin secretion, inhibits appetite centres in the brain as well as delays gastric emptying. It is used in the management of type 2 diabetes as well as obesity management. In a randomised controlled trial of 44 obese

binge eaters divided into 2 groups for 12 weeks, Robert SA *et al.* found participants who received liraglutide in addition to diet and exercise, showed significant improvement in binge eating, accompanied by reduction in body weight (94.54 ± 18.14 kg to 90.14 ± 19.70 kg, $p < 0.001$), BMI (36.15 ± 3.84 kg/m² to 34.40 ± 4.77 kg/m², $p < 0.001$), and waist circumference (103.9 ± 13.7 cm to 100.2 ± 14.0 cm, $p = 0.004$). On the other hand the control group showed slight but not significant changes in these parameters.¹³⁸

Robert *et al.* studied the effect of untreated fenugreek (*halba* in Malay) seed powder (5.5g) on a small sample (n=14) of overweight and obese individuals and reported that it decreased the post-prandial glycemic response and increased satiety.¹³⁹

Sibutramine is a serotonin-noradrenaline reuptake inhibitors (SNRI) related to amphetamines that suppresses appetite and is a prescribed weight reduction agent. It has been withdrawn in several countries due to concerns regarding its cardiovascular effects. A case of non-ischemic dilated cardiomyopathy in a man who lost approximately 10 kg in total in 4 months has been reported locally.¹⁴⁰

BIOMARKERS

Although over-eating and under-exercising are the main drivers for obesity, the physiological trigger to stop eating, that one might expect to govern this, appears not to be effective enough to overcome the tendency for humans to deviate from the ideal healthy body weight. The satiety effect of homeostatis is not coping with the socio-economic success that has produced abundance of food supply. Understanding the genes and biological pathways that control eating behaviour may provide a key to managing obesity.

A vast array of genes and their products including adiponectin, β 2-adrenoceptor (ADRB2), carnitine palmitoyltransferase-1 (CPT1), cholecystokinin, fat mass and obesity associated (FTO), ghrelin, glucagon-like-peptide-1 (GLP1), insulin-induced gene 2 (INSIG2), leptin, long-chain fatty acyl-coenzyme A (LCFA-CoA), melanocortin-4 receptor (MC4R), N-acylphosphatidylethanolamine (NAPE), neuropeptide Y (NPY), oleylethanolamide (OEA), oxyntomodulin (OXM), peptide YY (PYY), resistin, syndecan 3 (SDC3), and others act on the gut or brain to promote either anorexia or satiety. Many of these biomarkers may be associated with obesity related traits, even if they are not significantly associated with obesity itself measured by BMI.

In addition, inflammation, indicated by its various markers such as C-reactive protein, tumour necrosis factor and others also affect metabolism and obesity. Gut microbiota also plays a role.

Leptin is a satiety signal. Fan and Say investigated the prevalence of the leptin genes LEP (A19G) and LEP (G2548A) single nucleotide polymorphisms (SNPs) and the leptin receptor genes LEPR (K109R) and (Q223R) SNPs. The prevalence of the variant allele of the genes were 0.74, 0.67, 0.61 and 0.79 respectively. Indians had the lowest rates of the variant genes and Chinese had the highest. The variant

genes were not associated with obesity, but the LEPR (109R) SNP (rs1137100) variant was protective against obesity and subjects with the variant had lower plasma leptin levels than their wild-type allele counterparts. Chinese had the highest frequency of the variant.¹⁴¹ The leptin haplotype designated as GCCGGAA in a study by Apal Sammy, was associated with obesity in Malaysian Malays. Levels of leptin in plasma were also linked to obesity and metabolic abnormalities.¹⁴²

Apal Sammy also found blood adiponectin levels associated with obesity, but resistin appeared have less effect on obesity.¹⁴² Adiponectin levels in blood are highly associated with the ADIPOQ gene. Apal Sammy found a significant association between the ADIPOQ (rs17366568) gene variant and obesity among Malays. The frequencies of AG and AA genotypes were significantly higher in the obese group (11%) than in the non-obese group (5%). However, no significant association was found between allelic frequencies of the ADIPOQ (rs3774261) variant gene.¹⁴³ Apal Sammy found no association between the SNP (rs34861192) and (rs3219175) of the resistin (RETN) gene and obesity among Malay men.¹⁴⁴

The melanocortin-4 receptor (MC4R) mediates the effects of leptin in its anorexigenic pathway, and a defective gene that fails to suppress appetite is associated with obesity. Chua *et al.* found only a 0.02 frequency (10/498) of the Valine>Isoleucine variant (V103I) of the MC4R among subjects in Kampar and no significant difference related to obesity measurements.¹⁴⁵ Apal Sammy *et al.* found no significant association of the SNPs variants of MC4R; (rs571312), (rs2229616), (rs7227255) with obesity, even though the (rs571312), (rs2229616) SNPs were associated with obesity related parameters.¹⁴⁶

The Fatty Acid Binding Protein 2 (FABP2) is associated with insulin resistance and obesity in many populations. Among diabetics, Lee found the Alanine>Threonine variant of the FABP2 (Ala54Thr), was significantly associated with obesity among Indians (n=146), but not Chinese (n=133) and Malays (n=161).¹⁴⁷

Pro-opiomelanocortin (POMC) is a peptide that is cleaved to produce several food intake suppressing peptides. Lee *et al.* investigated the prevalence of the RsaI SNP in the 5'-untranslated region (UTR) of the POMC gene among Malaysians in Kampar, and found that the (-/-) variant occurred in 8.9% (27/302) of the subjects, and the frequency of the (-) allele was 0.31. There was no association of the (-) allele with obesity, nor gender or ethnicity.¹⁴⁸

The cocaine- and amphetamine-regulated transcript prepropeptide gene (CARTPT, Gene ID: 9607) encodes for a protein which modulates the anorectic pro-opiomelanocortin (POMC)/CART neurons in the hypothalamus. Some genetic variants of the CARTPT gene have been found to be associated with obesity. The CARTPT (rs2239670) variant gene has been shown to be associated with alcoholism among Koreans. Yeo *et al.* investigated that variant and found it is not a predictor for obesity among the Malaysian subjects.¹⁴⁹

Common variants in the fat mass- and obesity-associated (FTO) gene have been previously found to be associated with

obesity in various adult populations. Apal Sammy *et al.* found no significant allelic or genotypic type frequency difference for 31 FTO gene SNPs between 158 obese and 429 non-obese Malay Malaysian subjects.¹⁵⁰ One of these genes, FTO (rs9939609), was also examined by Chey *et al.* in a multi-ethnic population sample and reported that subjects with allele A had marginally but significantly higher waist circumference which was abolished when adjusted for age, gender and ethnicity.¹⁵¹

The insulin-induced gene 2 (INSIG2) plays a role in cholesterol metabolism, lipogenesis, and glucose homeostasis and studies have shown that INSIG2 polymorphisms were associated with obesity and weight gain. However, Apal Sammy *et al.* found no significant association between the (rs7566605) tagging SNP of INSIG2 with obesity or other metabolic parameters in the Malaysian Malay population.¹⁵²

Peptide Tyrosine-Tyrosine (PYY) is a hormone released in the intestinal tract to suppress pancreatic secretions and eventually reduce appetite. The R72T variant in the PYY gene (rs1058046) has been associated with increased susceptibility to obesity. Chan *et al.* found a 0.45 frequency for the variant T allele among 197 subjects in Kampar. Indians had the highest rates of the T allele (61.3%) and Chinese the lowest (32.5%). The rate in Malays was 49.3%. They found no association of genotype with obesity measured by BMI, but the TT genotype was associated with a higher waist circumference and visceral fat level.¹⁵³

β 2-Adrenergic receptors (ADRB2) play a role in blood pressure regulation, lipoprotein metabolism, energy expenditure and hence obesity. Apal Sammy *et al.* however found the gene variant ADRB2 (Gln27Glu)SNP (rs1042714), not significantly associated with BMI among Malays.¹⁵⁴

Osteocalcin, an osteoblast-specific protein, is a marker of bone formation but also influence body fat. Lack of osteocalcin has been associated with obesity. Chin *et al.* demonstrated that serum osteocalcin level was significantly associated with obesity and serum HDL cholesterol level in a sample of 373 Malaysian men.¹⁵⁵

Oxidative stress is induced in obesity. It is present when there is an imbalance between the antioxidant defence system and free radical production. Plasma total antioxidant capacity (TAC) is a biomarker derived to assess cumulative action of all the antioxidants present in plasma. Lim *et al.* measured the Trolox equivalent antioxidant capacity (TEAC) among 362 Malaysian subjects and determined that it was significantly associated with obesity.¹⁵⁶

The soluble form of the urokinase plasminogen activator surface receptor (suPLAUR) enhances leukocyte migration and adhesion, and its circulatory level is increased in inflammatory states. Of 3 variants, Ng *et al.* found that only suPLAUR(transcript variant 2) increases in omental adipose tissues in obese individuals, suggesting it has a role recruiting immune cells to adipose tissue in the pathogenesis of obesity.¹⁵⁷

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor proteins that play a role in the expression of genes that regulate metabolism. Chia *et al.* found none of the SNPs of PPAR they investigated were associated with obesity and Met-S in the suburban population of Kampar, Malaysia.¹⁵⁸

The uncoupling proteins (UCP) 1-3 are mitochondrial inner membrane proteins that can dissipate the proton gradient before it can be used to provide the energy. Lee *et al.* found that Chinese with the T allele of the UCP3 -55C/T single nucleotide polymorphism had significantly lesser risk to be centrally obese (OR=0.69).¹⁵⁹

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

It is clear that the effort to combat the high prevalence of obesity has been and is a national priority and resources must be allocated appropriately.¹⁶⁰ The Ministry of Health may educate and counsel its patients and contacts in all its health facilities and designate various professions, from doctor to nurses and dieticians to different roles in the course of regular work. It may also consider strategic programmes and campaigns. However, the national effort must be wider than that. Non-governmental organisation, schools, other government agencies and bodies, corporate firms, and community associations and societies and even religious groups can raise awareness as well as run programmes. This can be done when they are given motivational and technical assistance. The need is to educate the masses about what constitute healthy living and probably the mass media is the most powerful channel today. Radio, television, magazines and the internet have the most penetrating reach into all strata of society. Health is for all and proper nutrition is truly a matter in which every individual is a stakeholder.

The two main areas for action are food intake and physical activity. The low education and low income segment of the population need to be taught how to eat healthily and if they have issues concern access to such food, they should be given assistance. Housewives are obviously the key target population. They are not only one of the most obese occupational group, they control how the rest of the family eats. They should be taught what foods to buy and how many calories each meal should contain. The marketing and advertisement of cheap unhealthy food should be addressed. The level of physical activity among Malaysians might be addressed by focusing on the mode of transport of the average Malaysian. Transportation constitutes a significant part of daily activity and if instead of cars and motorcycles, more of the population can be encouraged to bicycle and use public transport, their level of physical activity would increase. Sporting activity in leisure time can be promoted and families can be involved together. Programmes on achieving exercise targets can be disseminated through the mass media and devices that help individuals track their physical activity level utilised more widely.

SECTION 3: FUTURE RESEARCH DIRECTION FOR OBESITY IN MALAYSIA

The prevalence of obesity in Malaysia has been fairly well established by numerous studies over the past decade but this should be followed up with well-timed surveys to monitor the changing trends. Prevalence studies in special groups should only be done and interpreted with reference to the overall data and have a clear interest, such as to identify groups with a particularly high prevalence and risk factors or problems such as dual malnutrition which require targeted intervention.

Alongside the programmes to manage obesity research needs to be conducted to monitor the outcome of obesity reduction programmes.

The MASO identified several areas of research needs in their report. They included measures for prevention of overweight and obesity in the local situation. They mentioned studies to determine the environmental, behavioural, social and ecological factors that contribute to obesity in different segments of the population. They listed studies to assess the economic burden of overweight and obesity in the population and behavioural research to identify culturally appropriate techniques to motivate people to increase and maintain physical activity and make healthier food choices. They also listed research on the influence of marketing practices in food industry and food outlets and cost-effectiveness of community-directed measures to prevent and manage overweight and obesity. The report also mentioned the need to assess community insights in relation to their understanding, perceptions, and expectations on weight maintenance.^{1,20}

Childhood obesity, which is outside the scope of this review also needs to be addressed, and the school setting plays an important role.

Researchers in Malaysia should keep abreast with new findings about biomarkers and where relevant study the significance of these biomarkers in our population.

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A Review of Metabolic Syndrome Research in Malaysia

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ABSTRACT

Seventy-three articles related to metabolic syndrome were found in a search through databases dedicated to indexing all literature with original data involving the Malaysian population between years 2000 and 2015. Metabolic syndrome affects 25 to 40% of adult population of Malaysia with the risk increasing with age. Obese children are also at risk. Indian ethnicity has the highest rates, followed by Malay and Chinese. It was found that socioeconomic determinants such as living in urban areas, unemployment, lower income, lower education level and shift workers had higher prevalence of metabolic syndrome. Metabolic syndrome is associated with other medical conditions like cardiovascular diseases, psychiatric disorders, erectile dysfunction, polycystic ovarian syndrome and colorectal cancer. Several biomarkers have been determined to be relevant to our local population but their usage in clinical setting needs further research. Literature into effectiveness of management of metabolic syndrome in Malaysia is lacking and the results were only modest. There are several diagnostic criteria available for metabolic syndrome internationally and their individual significant to our local population is not clear. It also makes it difficult to compare results between studies using different criteria. Finally, we could not identify any local study to look at the health economic burden of metabolic syndrome locally.

KEY WORDS:

Metabolic syndrome, risk factors, Malaysia, prevalence, biomarkers, obesity

INTRODUCTION

A literature search of articles as detailed in the paper *Bibliography of clinical research in Malaysia: methods and brief results*¹ using the medical subject heading (MeSH) Metabolic Syndrome X, covering period Jan 2000 - Dec 2015 (last search date 2 Feb 2016) was undertaken and 73 articles were identified. Data relevant to metabolic syndrome in Malaysia were reviewed below.

Metabolic syndrome, previously also known as Syndrome X,² is a disorder of energy utilization and storage reflecting underlying insulin resistance. It is characterised by the presence of at least three of the following five risk factors: Central obesity, high serum triglycerides, low high density lipoprotein cholesterol (HDL-C), raised blood pressure and raised fasting blood sugar. There are a number of slightly different diagnostic criteria, including the modified World Health Organization (WHO 1998)³ the International

Diabetes Federation/National Heart, Lung and Blood Institute/American Heart Association, (IDF/NHLBI/AHA-2005) criteria,⁴ the revised National Cholesterol Education Program (NCEP ATPIII) 2001⁵ and 2005⁶ and the Joint Interim Statement (JIS 2009) or “harmonized” criteria.⁷ Depending on the guidelines used the prevalence of metabolic syndrome can vary.

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY

Adult prevalence

One of the earliest works done to estimate the prevalence of metabolic syndrome in Malaysia was to look at the prevalence of clustering of hypertension, abnormal glucose tolerance, hypercholesterolemia and obesity among Malaysians. Using the National Health and Morbidity survey (NHMS) 1996, Lim *et al.* reported 27% of their study population above 30 years have two or more of the risk factor clusters.⁸ Another study that investigated the prevalence of all the components of metabolic syndrome before most of the common definitions were formulated was that by Hapizah *et al.*⁹

Subsequent studies showed that the overall prevalence of metabolic syndrome among adults in Malaysia lies between 25-40%, depending on the criteria one uses. For example based on the WHO, IDF, NCEP ATP III (2001) and Harmonized (JIS) definitions, according to Wan Nazaimoon *et al.*, the overall crude prevalence of metabolic syndrome was found to be 32.1%, 37.1%, 34.3%, and 42.5% respectively, in a nationwide, cross-sectional study using a two-stage stratified sampling design of 4,341 subjects across Peninsular and East Malaysia in 2008.¹⁰ The largest study, Rampal *et al.*, carried out in 2004, found that the overall prevalence for metabolic syndrome was 27.5% among those >15 years old using the IDF criteria.¹¹ The prevalence of metabolic syndrome in Malaysia is high relative to Asian countries.^{10,11} Table I gives the rates recorded in various studies.

In the Malaysian context, there was stronger correlation between Harmonised (JIS) and IDF definitions (Kappa index, 0.87-0.99),^{15,19} moderate correlation between Harmonised (JIS) and NCEP ATPIII (2001) definitions (Kappa index 0.86)¹⁵ and IDF and NCEP ATP III definitions (Kappa index, 0.58-0.68)^{12,17,19} but a poor correlation between the IDF and modified WHO criteria (Kappa index, 0.26-0.31).^{12,17}

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Table I: Prevalence of metabolic syndrome in Malaysia by different diagnostic criteria according to various investigators

Author (Year of study)	Sample Size	Characteristics	Prevalence of Metabolic Syndrome by different criteria (%)				
			WHO	IDF	NCEP ATP III 2001	NCEP ATP III 2005	Harmonized (JIS)
Rampal <i>et al.</i> ¹¹ (2004)	18,805	>15yrs Pen Malaysia and Sarawak		27.5			
Tan AKG <i>et al.</i> ¹² (2005-06)	2,366	25-64 yrs		30.1		36.1	
Wan Nazaimoon <i>et al.</i> ¹⁰ (2006)	4,341	>18 yrs Pen Malaysia and Sabah	32.1	37.1	34.3		42.5
Moy & Bulgiba ¹³ (2008-09)	1,494	University staff >35 yrs Malays		38.2		41.4	
Chu & Moy ¹⁴ (2010-11)	686	University staff >35 yrs Malays				31.9	
Heng <i>et al.</i> ¹⁵ (2012)	227	University staff 20-65 yrs Malays		38.8	33.5		38.3
Tan BY <i>et al.</i> ¹⁶	109	Opportunistic contact 30-65 yrs KL and Selangor	6.4	22.9	16.5		
Zainuddin <i>et al.</i> ¹⁷	298	Villagers 18-59 yrs Kelantan		32.2	28.5		
Tan M <i>et al.</i> ¹⁸	1,046	Men >40 yrs Subang Jaya		31.6			
Ramli <i>et al.</i> ¹⁹	8,836	Urban and Rural >30 yrs Pen Malaysia and Sabah		37.4	26.5		43.4
Chee <i>et al.</i> ²⁰	675	Government employees >20 yrs Putrajaya		46.3	27.9		48.9

Table II: Prevalence of Metabolic Syndrome by age, gender and ethnicity among Malaysians ≥15 years by IDF criteria, 2004.¹¹

	Prevalence (%)		
	Female	Male	Total
Age 15-40 years			
Malays	15.7	14.7	15.2
Chinese	13.9	13.4	13.7
Indians	23.3	21.8	22.5
Indigenous Sarawakians	26.3	22.1	24.2
Age >40 years			
Malays	51.5	38.5	45.0
Chinese	45.4	36.3	40.8
Indians	64.9	51.3	58.3
Indigenous Sarawakians	47.2	34.4	40.6

Cheong *et al.* have explored whether waist circumference (WC), body-mass index (BMI) or waist-to-hip ratio (WHC) was better at predicting the presence other metabolic syndrome factors in the Malaysian population and found that BMI and WC were better than WHR with WC slightly superior.²¹

Age

The prevalence of metabolic syndrome increases with age.^{8,10,11,15,18} Under the age of 40 years, the prevalence rate does not exceed 25% but above the age of 40 years, it rises to over 40% (Table II). Wan Nazaimoon *et al.* and Chee *et al.* estimated that the risk of metabolic syndrome increased by 3% for every year increase in age.^{10,20}

Sex

Table II from Rampal *et al.* shows that females have a higher prevalence of metabolic syndrome. Overall the prevalence was 30.1% among females and 24.1% among males.¹¹ Wan

Nazaimoon *et al.* also found metabolic syndrome more prevalent among women (43.7%) than men (40.2%).¹⁰ Ramli *et al.* found females had a higher age-adjusted prevalence according to the NCEP-ATP III 2001 (24.1% vs 28.9% and IDF (36.1% vs 39.3%) criteria but not according to the Harmonised (JIS) definition (43.8% vs 43.9%).¹⁹ In another report from rural Kelantan²² of the same study by Zainuddin *et al.*¹⁷ it was noted women had a higher prevalence of metabolic syndrome. This was true by either the Harmonised (JIS) (29.8% vs 42.9%) IDF (26.6% vs 36.6%) or NCEP ATP III 2001 (20.2% vs 34.3%) definitions.¹⁶

In contrast, among urban Malays, Heng *et al.* found the prevalence higher among men, in all age groups by all three criteria they investigated, especially those below 40 years¹⁵ as did Moy and Bulgiba.¹³ The prevalence Moy and Bulgiba noted their study of Malay men and women was (52.9% and 47.1% by IDF criteria. The gap was even wider (men 54.7%, women 45.3%) by the NCEP ATP III 2005

criteria).¹³ Chu and Moy recorded similar findings (men 37.1%, women 24.2%).¹⁴ Heng *et al.* noted a steeper rise in the prevalence of metabolic syndrome with age among women.¹⁵ All three studies however involved urban populations specifically. Similarly Chee *et al.* found a higher prevalence of metabolic syndrome among men (57.1%) than women (46.3%) government servants in Putrajaya, by the Harmonized criteria.²⁰ Abdominal obesity was more prevalent among women and hypertension more prevalent among men.

Tan AKG *et al.* found the prevalence was about equal between men and women.¹² It would appear that the differences in the prevalence of metabolic syndrome seen between genders depended on where the study subjects were recruited. Our local data suggests that in urban areas, men have a higher prevalence of metabolic syndrome, while in rural areas women exceed men. In addition, the differences are also dependent on the metabolic syndrome criteria used. For example, Tan AKG *et al.* found that the prevalence was higher in men than women (37.2% vs 35.3%) by the NCEP ATP III 2005 guidelines, but was the reverse (28.5% vs 31.2%) using the IDF guidelines.¹² The IDF criteria gives more weight to central obesity and females in Malaysia were more likely to suffer from central obesity^{19,23} and have higher hip circumference compared to men.²⁴ In contrast, waist circumference and waist-hip ratio were higher in men, in a study by Azwany *et al.* to determine which factors contributes most to having metabolic syndrome.²⁴

Ethnic Differences

Indians, both men and women, have the highest rates of metabolic syndrome compared to other ethnic groups in Malaysia.^{10,12,13,16,18,19} Malays were shown to have higher incidence compared to Chinese in some studies^{8,10,11,16,19} while data from the Malaysia Non-Communicable Disease Surveillance 2005/2006 did not showed significant difference.¹²

Interestingly, within the Indigenous Sarawakians, there appears to be a marked variation in the incidence between the young and the older generation, with people below age of 40 having a higher rate at 40.6% compared to their older counterparts at 24.2%. Further study is needed to answer this difference. No data was available for the Sabah state.¹¹ The Indigenous women in four Temuan villages in Selangor showed an incidence rate of 22.7%.²⁵

It is noteworthy that studies using different criteria of metabolic syndrome may yield different results even in the same cohort subjects. For example, in one study by Tan AKG, Chinese males were more likely to exhibit metabolic syndrome if NCEP ATP III criteria was used instead of IDF criteria. While like others, they found Indian males (42.3%) had a higher prevalence of metabolic syndrome than Chinese (31.3%), by the IDF criteria, the difference was much smaller (44.2% vs 42.4%) by the NCEP ATP III.¹²

Nevertheless, Tan AKG *et al.* attempted to explain the ethnic disparities of metabolic syndrome in Malaysia. It was shown that Indians were less likely to engage in physical activity

and to consume less fruit and vegetable.¹² Although education and family history of chronic disease are associated with metabolic syndrome status, differences in socioeconomic attributes do not explain ethnic disparities in metabolic syndrome incidence.

Geographical and Socio-economic Factors

Wan Nazaimoon *et al.* noted that, regardless of the criteria used, metabolic syndrome was higher in urban areas.¹⁰ Abdominal obesity was most prevalent (57.4%), was higher in females (64.2%) and was highest in Indians (68.8%). Hypertension was higher in males (56.5%) and highest among Malays (52.2%). In contrast, the Chinese had the highest prevalence of hypertriglyceridemia (47.4%). Lim *et al.* also found that urban residents, individuals with higher income and physical inactivity were associated with increased prevalence.⁸ Zalilah *et al.* on the other hand, found that metabolic syndrome was higher among women in low income rural communities (32%) compared to low income urban communities (19%) in a sample of 625 reproductive-age women from across Malaysia.²⁶ They also found metabolic syndrome higher among low income Malays (25%) than Indians (19%). It did not vary with food security status. In rural Kelantan, being a housewife or unemployed, having less income and education was significantly correlated with having metabolic syndrome.²¹

Nazri *et al.* found a trend of increasing prevalence of the markers of metabolic syndrome among shift workers compared to day workers which reached statistical significance for those with three or more markers.²⁷ Moy *et al.* also reported higher rates of metabolic syndrome factors among health care shift workers.²⁸

Obesity

Termizy and Mafauzy found that only 40.2% of 102 of their mainly Malay (94%) patients at their obesity clinic (BMI >30) fulfilled the IDF guidelines for metabolic syndrome.²⁹ The comorbidity prevalence for raised fasting blood glucose was 17%, followed by 36% for high triglyceride, 40% for reduced HDL and 42% for raised blood pressure. There was no linear correlation for obesity and metabolic syndrome. Class II obese (BMI 35-39.9) patients had a 1.43 higher risk compared to Class I obese (BMI 30-34.9) but Class III obese (BMI >40) had only a 1.23 higher risk. The prevalence in obese females (43.7%) was higher than for males (32.3%).

Diabetes

Tan MC *et al.* found that 96.1%, 95.8%, 84.8% and 97.7% of 313 of their diabetic patients aged ≥30 years had metabolic syndrome using NCEP ATP III, WHO, IDF and Harmonized definitions, respectively.¹⁷

Physical Activity

Chu and Moy found that subjects who sat for ≥9.3 hours a day had a 3.8 fold risk of having metabolic syndrome compared to those who sat ≤6 hours a day.¹⁴ Chee *et al.* found that those in the 'maintenance' stage of doing regular exercise were 17 times less likely to have metabolic syndrome compared to those who have not even contemplated exercising.²⁰

Children and Adolescents

It is very unlikely to find metabolic syndrome among non-obese children.

In a small sample of 78 involving children of 8-10-year olds, of whom 43.6% (34/78) were obese, Quah *et al.* found only 1 obese child with metabolic syndrome by the IDF criteria.³⁰ Metabolic syndrome was found in 5.3% of the overweight/obese children but none of the normal-weight children, in a case-control study of 402 normal weight compared with overweight/obese 9-12 year old children in Kuala Lumpur in 2008 using the IDF criteria.³¹ They were sampled from a 2,770 school children of whom 30.9% were overweight and 3.3% obese. Indians again were found to have highest odds ratio (OR = 5.5) for metabolic syndrome. Overweight/obese girls had a 2.5 times higher risk of metabolic syndrome compared to boys.

Fadzlina *et al.* found a 10% prevalence of metabolic syndrome among the 280 (25.4%) overweight 13-yr old school children, out of a sample of 1,104, in the West coast of Peninsula Malaysia using the IDF criteria.³² The overall prevalence was 2.6% (males=3.4%, females=2.1%). None of the normal weight had metabolic syndrome. Those who had a habit of sleeping 7-9 hours had a lower risk of having metabolic syndrome compared to those who slept either more or less.

By the NCEP ATP III criteria, metabolic syndrome was diagnosed in 30.4% of 335 obese adolescent boys and girls aged 12-18 years from 10 randomly selected schools in Penang.³³ More than 90% of obese adolescents had at least one metabolic abnormality. Metabolic syndrome was more prevalent among obese boys (40.2%) compared to obese girls (17%). Boys had significantly higher mean waist circumference and triglycerides and lower HDL-C. Indians had the highest prevalence of metabolic syndrome (36.4%), followed by Chinese (33.8%) and Malays (27.4%). Elevated triglyceride levels were more prevalent among Chinese, hypertension more prevalent among Malays, and the other three abnormalities among Indians.

Elderly

The prevalence of metabolic syndrome was 43.4% in a sample of 343 elderly (>60 yrs) residing low cost flats in an urban area in the central of Malaysia according to the IDF criteria.³⁴ More women (48.1%) were affected than men (36.3%). Being obese or overweight was the strongest predictor. High carbohydrate intake increased risk of metabolic syndrome in men 2.8 fold. In women, higher fat free mass index (3.9), physical inactivity (2.1) and good appetite (2.3) increased the risk of having metabolic syndrome.

ASSOCIATED DISEASES

Cardiovascular Diseases

Metabolic syndrome is of course known for its nature to increase cardiovascular disease risks. Yeow *et al.* have shown that it significantly increases other markers of cardiovascular risks such as HbA1c, albumin: creatinine ratio and highly sensitive C-reactive protein.³⁵ Mas Ayu *et al.* reported that

metabolic syndrome increased the score of the Framingham Risk Score for cardiovascular disease among Malaysian patients with schizophrenia.³⁶ Aminuddin *et al.* determined that the carotid femoral pulse wave velocity (PWVCF), a measure of arterial stiffness, and high-sensitivity C-reactive protein (hs-CRP), was significantly higher among metabolic syndrome vs healthy participants in study of volunteers recruited via advertisement. The Augmentation index (AI), a measure of wave reflection that arrives back to the aorta after the forward wave and another measure of arterial stiffness, was not significantly different. There was a significantly higher AI value for metabolic syndrome individuals by the Harmonized criteria, but that disappeared when adjusted for race. The AI was significantly higher in Malays compared with Chinese.³⁷

Psychiatric Disorders

Even before metabolic syndrome was recognized as an entity, it had been noticed that psychotic patients had high rates of obesity and type 2 diabetes. This was thought on account of several reasons, including an inactive lifestyle, poor dietary choices and side effects of antipsychotic medications.³⁸ Not surprisingly when schizophrenics are surveyed they have been found to have a higher than normal prevalence rates of metabolic syndrome, as by Mas Ayu *et al.* (46.7%, 126/270, by NCEP ATP III (2001) criteria).³⁶ In a further report these investigators noted that for patients on monotherapy, the average prevalence of metabolic syndrome was higher for patients on the seven different types of first generation antipsychotics studied compared to the seven different types of second generation antipsychotics.³⁹ Elevated fasting blood glucose was the least common metabolic syndrome component encountered. Atypical antipsychotics differ markedly in their risk to cause metabolic disturbance and caution is needed when prescribing these agents to patients with psychosis.⁴⁰

Roffeei *et al.* found that the A allele of the FTORs9939609 T>A gene, the G allele of the LEPRrs1137101A>G gene and the T allele of the MTHFRrs1801133C>G gene were associated with metabolic syndrome in a sample of 206 outpatient schizophrenic patients of whom 59.7% (123/206) had metabolic syndrome. They found no association for polymorphisms of the ADIPOQ, ADRA2A, BDNF, DRD2, HTR2A, HTR2C, LEP, MC4R and PMCH genes.⁴¹

On the other hand, in a very small study, Abdul Hamid *et al.* found that 13/31 (41.9%) of their mood disorder patients had metabolic syndrome by the IDF criteria compared to only 3/20 (15%) of their schizophrenic patients.⁴² They noted having antipsychotic therapy was not associated with prevalence of metabolic syndrome. Hat *et al.* observed that 37.5% of their sample of patients with major depressive disorders had metabolic syndrome by the IDF criteria.⁴³ Neither severity of depression nor any type of medication was significantly associated with metabolic syndrome.

Erectile Dysfunction/Testosterone Deficiency

Tan WS *et al.* found 20.8% prevalence of self-reported erectile dysfunction and 16.0% of biochemical testosterone deficiency among a sampled population of men from Subang Jaya. All the components of metabolic syndrome were significantly

associated with both erectile dysfunction and testosterone deficiency.¹⁸ Chin *et al.* also showed testosterone and sex hormone-binding globulin levels were significantly reduced in metabolic syndrome male subjects compared to non-metabolic syndrome subjects.⁴⁴

Polycystic Ovarian Syndrome

Kulenthiran and Majeed have also shown a strong correlation between polycystic ovarian syndrome and glucose intolerance, obesity and dyslipidaemia, in a cross-sectional case-control study of Malaysian women, although they did not apply all the factors of the various definitions of metabolic syndrome.⁴⁵ They note that the association between insulin resistance and polycystic ovarian syndrome is well-established, although its pathogenesis is still elusive.

Gestational Diabetes

Shyam *et al.* screened 77 (out of 304) women aged between 20-40 years (mean 30.5 years) with gestational diabetes, who had either a family history of diabetes, dysglycemia and/or central obesity 2-6 months after delivery for metabolic syndrome. They found 22% (17/77) had metabolic syndrome by the Harmonized criteria.⁴⁶

Colorectal cancer

Ulaganathan *et al.* have observed that having metabolic syndrome was associated with a 2.25 times risk of having colorectal cancer in a case control study in Malaysia.⁴⁷ Colorectal cancer patient had a 70.7% prevalence of metabolic syndrome compared to a 39.3% prevalence among controls. The more components of metabolic syndrome an individual had the high the risk for colorectal cancer.

MANAGEMENT

Nutrition

Shahar *et al.* tested a nutrition education intervention programme among elderly (>60yrs) rural Malays with metabolic syndrome delivered via group counselling sessions, talks, and cooking and exercise demonstrations. Assessed at 3 and 6 months, the only significant finding was a decrease in WC among women (from a mean 104 cm to 100 cm) in the intervention group (n=14) versus the control group (n=12). Mean values of the parameters of metabolic syndrome did improve in the intervention group, but only marginally.⁴⁸

Teng *et al.* observed that both amount and type of dietary fats alter thrombogenic factors, but only the amount of dietary fatty acids affects postprandial lipemia among subjects with metabolic syndrome.⁴⁹

Physical activity

There is growing evidence that regular physical activity favourably affects component factors of metabolic syndrome. Chee *et al.* conducted an interventional trial among employees of government agencies in Putrajaya, with metabolic syndrome, who regularly logged in to Facebook. 120 participants completed the programme after they were randomised into two groups. One group received weekly posts to promote physical activity. Each member of both groups received a pedometer and both groups had fortnightly meetings. The Facebook group increased their number of

steps per day by 3,295 (84.5%) from baseline, while the control group showed an increase of 520 (13.2%) steps after four months. The Facebook page was then deactivated. After two months the Facebook groups was still recording 2,264 (58.1%) steps above baseline while the control group recorded 379 (9.6%) extra steps daily. A correlation was seen between the change in the number of steps taken daily and improvement in all measurements of metabolic syndrome. There was a 94.3% reduction in metabolic syndrome in the Facebook group after four months compared to 21.2% in the control group. After two more months the prevalence of metabolic syndrome rose 5.7% in the Facebook group and 9.4% in the control group.⁵⁰

BIOMARKERS

Adiponectin, an adipocyte-secreted cytokine, which possesses insulin-sensitizing properties, is thought to play a role in the metabolic syndrome. Adiponectin levels decrease with obesity. Low *et al.* found a significantly lower adiponectin levels in overweight/obese compared to normal/underweight pregnant mothers in their first trimester in a small study of 104 subjects in Selangor.⁵¹ Lau and Sekaran have found low adiponectin levels (hypoadiponectinemia) strongly associated with metabolic syndrome and also with type 2 diabetes.⁵² The mean value of serum adiponectin was 9.13 µg/ml among controls compared with 7.22 µg/ml among subjects with metabolic syndrome and 6.51 µg/ml among subject with both metabolic syndrome and type 2 diabetes. Another case-control study by Aznan *et al.* also found significantly different mean adiponectin levels among healthy respondents (13.21 ± 3.88 mmol/l) and subjects with metabolic syndrome (11.64 ± 4.26 mmol/l).⁵³

The adiponectin polypeptide, with 244 amino acids, is encoded by the *ADIPOQ* gene on chromosome 3q27.3. More than 30-70% of the variability of the blood levels of adiponectin are thought to be explained by genetics.⁵⁴ Several single nucleotide polymorphisms (SNP) are associated with hypoadiponectinemia in some populations. Lau and Sekaran found that none of the single nucleotide polymorphisms *ADIPOQ* SNP+45T>G, SNP+276G>T, SNP+639T>C and SNP+1212A>G influence circulating levels of adiponectin in Malaysian men.⁵⁵ When examining the allelic variants, they found variants of certain alleles associated with elevated LDL levels, blood pressure, plasma glucose or waist circumference. However there was no conclusive link between SNP+45T>G and SNP+276G>T with traits related to metabolic syndrome. However the C allele of SNP+639T>C and the G allele of SNP+1212A>G were associated with increased risk of dyslipidemia, hyperinsulinemia and obesity among Malay men.⁵⁶

Resistin, a macrophage-derived polypeptide, conversely, has been shown to be up-regulated in subjects with insulin resistance. Lau and Sekaran found high levels of resistin (hyperresistinemia) strongly associated with metabolic syndrome and with type 2 diabetes.⁵² The mean value of serum resistin was 14.39 ng/ml among controls compared with 15.78 ng/ml among subjects with metabolic syndrome and 27.05 ng/ml among subjects with both metabolic syndrome and type 2 diabetes. They derived an adiponectin-

resistin (AR) index that was more strongly associated with increased risk of type 2 diabetes and metabolic syndrome than neither hypoadiponectinemia or hyperresistinemia alone.⁵²

The resistin polypeptide, with 108 amino acids, is encoded by the RETN gene on chromosome 19p13.2. It is estimated that up to 70% of the variation in circulating resistin levels can be explained by genetic factors.⁵⁷ Lau and Sekaran found that the SNP variants SNP-420C>G and SNP+299G>A of the resistin gene were strongly associated with serum resistin levels. For the SNP-420C>G variants, the G/G genotype had the highest serum resistant levels. For the SNP+299G>A it was the A/A genotype who had the highest levels.⁵⁵ They also showed that the G allele of SNP-420C>G and the A allele of SNP+299G>A were associated with increased risk of hyperglycaemia among Chinese, and impaired beta-cell function and insulin sensitivity among Indians.⁵⁶

Plasma plasminogen activator inhibitor-1 (PAI-1) the primary physiological inhibitor of endogenous fibrinolysis acts via inhibition of **tissue plasminogen activator (tPA)** and **urokinase type activator (uPA)**, often leading to fibrin accumulation in basement membranes and interstitial tissues. Increased PAI-1 and decreased tPA promotes thrombosis and is associated with metabolic syndrome. However, the cardiovascular risks of raised PA-1 disappear when adjustments for the markers of metabolic syndrome are made, suggesting raised PA-1 is a consequence of metabolic syndrome rather than its cause. Al-Hamodietal. have found PA-1 activity high in metabolic syndrome subjects, with or without type 2 diabetes in a case-controlled study compared with non-metabolic syndrome subjects, with and without type 2 diabetes respectively.⁵⁸ tPA activity negatively correlated with its antigen.

Several SNPs in the PAI-1 gene have been identified, among which is the 4G/5G polymorphism (in the 4G allele at 3' end the 5th G is replaced by A). Al-Hamodietal. have found in a study of 126 Malaysian subjects that carriers of the 4G/4G allele have the highest PA-1 activity and carriers of the G5/G5 allele the lowest.⁵⁹ Heterozygous 4G/5G have values closer to 4G/4G. 4G/4G individuals were most prone to metabolic syndrome.

Hepatocyte nuclear factor 4 (HNF4) alpha

Polymorphism of the hepatocyte nuclear factor 4(HNF4) alpha gene is thought to be associated with insulin resistance and metabolic syndrome. Saif-Ali *et al.* have found the single nucleotide polymorphisms(SNP) rs1885088 of the HNF4 alpha gene to be associated with type 2 diabetes with metabolic syndrome in Malaysians, while other SNPs were associated with diabetes without metabolic syndrome.⁶⁰

Vitamin D

Moy and Bulgiba noted vitamin D insufficiency was associated with metabolic syndrome in a sample of 380 Malay employees of a public university(OR=1.73).⁶¹ The oxidative stress of metabolic syndrome is postulated to have the potential to damage bone-forming osteoblasts. Mixed

results have been observed in bone mass measured by dual-energy x-ray absorptiometry (DEXA) and calcaneal quantitative ultrasonometry(QUS) in men. Chin *et.al.* found no difference in calcaneal speed of sound between those with metabolic syndrome and healthy respondents in a cross-sectional study of 309 men in the Klang valley.⁶²

Osteocalcin

Shyam *et al.* found that low osteocalcin was associated with diabetes but not adiposity in subjects with metabolic syndrome and central obesity.³

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Metabolic syndrome may be viewed as part of a spectrum of cardiovascular disease from normality to overt diseases such as diabetes mellitus, hypertension, coronary artery disease and stroke. It is interesting to know that there are many genetic and advance biomarkers that are associated with metabolic syndrome. The increasing knowledge of these biomarkers enables us to understand the basic science of the condition better. However, in clinical practice, the ultimate aim in managing cardiovascular disease is to prevent end organs involvement, to improve survival and to improve quality of life. The clinical relevance of biomarkers in this context is not evident. The metabolic syndrome is a syndrome developed to help in predicting cardiovascular diseases that uses easily measurable clinical parameters and a simple blood triglyceride level and our focus should be as such.

However, the existence of several metabolic syndrome definition makes it difficult for us to compare and communicate between research data. For example, different criteria give us different prevalence of metabolic syndrome amongst different ethnicity even in the same cohort. There are differences in waist cut-offs measurements between the Caucasians and Asians. However, we do not know whether this difference is presence between our ethnic groups and if so, how significant it is. In fact, the mismatch of incidence between metabolic syndrome and diabetes among different ethnic groups in Malaysia may be partially explained by the current metabolic syndrome definition used. Lower central obesity cut-off for Malays would improve the match between the incidence of metabolic syndrome and diabetes between Malays and Chinese in this country.

We do not know about our population awareness of metabolic syndrome and its risk factors. Like any non-communicable disease, we need to understand the healthcare providers and public perception and knowledge of the condition before any successful interventional programme could be planned. In addition, any successful intervention would probably need multidimensional approach. Therefore, it is not surprising that a unilateral approach management in the available literatures were only able to show very modest results.

SECTION 3: FUTURE RESEARCH DIRECTION

Clinically relevant research in the field of metabolic syndrome is much lacking comparing to magnitude of

burden of this condition in this country. We need consensus on the criteria of metabolic syndrome that is best suited for our population in order to allow better comparison and merging of data. Validation of waist cut-offs measurement in our population may improve definition of metabolic syndrome for local use better. Studies should be done to look into our population awareness of metabolic syndrome and its risk factors. More research into effective management programme will help us to tackle the metabolic syndrome problem better. However, multidisciplinary management approach would probably gather more useful knowledge than a unidisciplinary approach. Finally, research into the health economic burden of metabolic syndrome in this country will help the policy makers plan health resource better.

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APPENDIX 1: Definition of Metabolic Syndrome by different criteria

Risk factors (RF)	Modified WHO	NCEP-ATP III (2001)	IDF (2005)	NCEP-ATP III (2005)	Harmonised JIS (2009)
Obesity	BMI >30kg/m ² or Waist-hip ratio M>0.9 F>0.85	Waist Circumference M ≥102 cm F ≥88 cm	Waist Circumference M ≥90 cm F ≥80 cm	Waist Circumference M ≥90 cm F ≥80 cm	Waist Circumference M ≥90 cm F ≥80 cm
Blood Pressure	Systolic BP ≥140 and/or diastolic BP ≥90 mmHg or on treatment for HPT	Systolic BP ≥130 and/or diastolic BP ≥85 mmHg or on treatment for HPT	Systolic BP ≥130 and/or diastolic BP ≥85 mmHg or on treatment for HPT	Systolic BP ≥130 and/or diastolic BP ≥85 mmHg or on treatment for HPT	Systolic BP ≥130 and/or diastolic BP ≥85 mmHg or on treatment for HPT
Fasting plasma glucose	≥6.1 mmol/L or previously diagnosed T2DM	≥6.1 mmol/L or previously diagnosed T2DM	≥5.6 mmol/L or previously diagnosed T2DM	≥5.6 mmol/L or on treatment for T2DM	≥5.6 mmol/L or on treatment for T2DM
Triglycerides	>1.69mmol/L	≥1.7 mmol/L	≥1.7 mmol/L or on treatment for TG	≥1.7 mmol/L or on treatment for TG	≥1.7 mmol/L or on treatment for TG
HDL-C	M<0.90 mmol/L F<1.0 mmol/L	M <1.03 mmol/L F <1.29 mmol/L	M <1.03 mmol/L F <1.29 mmol/L L or on treatment for HDL-C	M <1.03 mmol/L F <1.29 mmol/L L or on treatment for HDL-C	M <1.0 mmol/L F <1.3 mmol/L L or on treatment for HDL-C
Metabolic syndrome definitions	Fasting plasma glucose ≥6.1 mmol/L+ 2 or more RF	At least 3 RF	Waist Circumference + 2 or more RF	At least 3 RF	At least 3 RF

A Review of Smoking Research In Malaysia

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ABSTRACT

Two hundred and seventy one original published materials related to tobacco use were found in a search through a database dedicated to indexing all original data relevant to Medicine and Health in Malaysia from 1996 - 2015. A total of 147 papers were selected and reviewed on the basis of their relevance and implications for future research. Findings were summarised, categorised and presented according to epidemiology, behaviour, clinical features and management of smoking. Most studies are cross-sectional with small sample sizes. Studies on smoking initiation and prevalence showed mixed findings with many small scale studies within the sub-groups. The majority of the studies were related to factors that contribute to initiation in adolescents. Nonetheless, there are limited studies on intervention strategies to curb smoking among this group. There is a lack of clinical studies to analyse tobacco use and major health problems in Malaysia. In addition, studies on the best treatment modalities on the use of pharmacotherapy and behavioural counselling have also remained unexplored. Reasons why smokers do not seek clinic help to quit smoking need further exploration. A finding on the extent of effort carried out by healthcare providers in assisting smokers to make quit attempts is not known. Studies on economic and government initiatives on policies and tobacco use focus mainly on the effects of cigarette bans, increased cigarettes taxes and the influence of the tobacco industry. Recommendations are given for the government to increase efforts in implementing smoke-free legislation, early and tailored interventions. Clinical studies in this area are lacking, as are opportunities to research on ways to reduce smoking initiation age and the most effective quit smoking strategies.

KEY WORDS:

Smoking, Review, Malaysia, Risk Factors, Initiation, Cessation

INTRODUCTION

Studies on smoking related material were reviewed to cover epidemiology, behaviour, clinical features and management of smoking. We conducted an extensive literature search in a database dedicated to indexing all original data relevant to Medicine and Health in Malaysia from 1996 - 2015 using the medical subheadings MeSH 'Smoking; Tobacco Use; Tobacco Smoke Pollution; Tobacco Use Cessation; Tobacco Use Disorder; Smoking Risk Factors; Smoking Initiation; Smoking Cessation; Malaysia'.

Of these, we initially reviewed 257 articles, 8 reviews, 4 theses, 4 books and 2 case studies. A total of 147 papers were selected and reviewed on the basis of their clinical relevance and implications for future research.

In this review, all types of studies were considered including journals articles, conference proceeding, guidelines and reports, single case studies, case series reports and reviews. The study design for most articles that were reviewed was cross-sectional using questionnaire survey targeting adolescents at schools and university students. A significant few were follow-up studies, intervention and population studies and smokers from specific groups (female smokers, health staff, civil servants, etc.) as well as smokers attending quit smoking clinics.

This review aims to examine the published studies conducted in Malaysia from 1996 to 2015. It is expected to provide an overview of research interest, its contribution to current practices and identify gaps in smoking research in Malaysia.

SECTION 1: REVIEW OF LITERATURE

EPIDEMIOLOGY

Smoking Prevalence

In Children and Adolescents

In Malaysia, there are 5 million smokers who are classified as children or adolescents younger than 18 years old as of 2010. In the past decade, the prevalence of cigarette smoking among male secondary school children was 33.2% who were current smokers² within the ranges 29.7% to 43.0%,³ with a male to female proportion of 63.5% to 17.5%.⁴ This is consistent with the highest prevalence of smoking found among schoolboys from the vocational schools.⁵ In a longitudinal knowledge, attitude and practices study among form 5 students over 1 year, the prevalence decreased from 29.7% to 26.7% after a year.⁶

The prevalence of smoking among secondary school students in Sarawak is 32.8% although the majority (96.9%) did not smoke on a daily basis.⁷ The prevalence of smoking was 22.8% among Form 6 students in the Petaling District, Selangor.⁸

In a study among primary school children in Tumpat, Kelantan, the reported smoking prevalence was 11.8%. Of these, 3.8% were current smokers.⁹ In a study of 190 secondary four male school students from three schools in

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Kota Bharu, 57 (30.0%) students were current smokers, 45 (23.7%) students were ex-smokers and 88 (46.3%) reported never smoking cigarettes.¹⁰ Overall prevalence of smoking was 6.7% amongst Malay adolescents in Kota Bharu.¹¹

The prevalence of future intention to smoke among adolescents current smokers was 10.7%.¹² The estimated prevalence of self-reported cigarette smoking among private university students was 10.3% to 29.0%.¹³⁻¹⁴

Smoking prevalence among lower secondary students of schools located in the Federal Land Development Authority (FELDA) settlement areas (42.9%) was two-fold higher than in the rural and town schools combined (20.3%)¹⁵ and confirmed by other studies.^{3,16} This situation will contribute to high smoking-related health problems in the future if proper preventive measures are not taken accordingly.³

In Adults

The prevalence of current smoking among adult males in 2006, in Malaysia is 46.5% (95% CI: 45.5–47.4%), which was 3.0% lower than a decade ago.¹⁷ The prevalence of current smoking among both male and female Malaysian adults aged 15 years and above is 23.1%,^{18,19} and is highest in those aged 21-30 years old.¹⁷

In the Elderly

The prevalence of smoking amongst the elderly (60 and above) was 39.2%.²⁰ Smoking is highly prevalent (39.2%) among elderly males in Malaysia and is higher compared to the United States (12.0%) and China (26.0%).²⁰

Smoking and Gender

Being male has been significantly associated with tobacco use.²¹⁻²⁴ The prevalence of smoking is higher in males than in females,^{4,6,11,16,25-29} with males starting smoking at younger age.^{6,28,30} One fifths of male adolescents smoke daily for more than three years.⁵

The prevalence of smoking in lower secondary school males was 35.5%.¹⁵ More than 50.0% of male students in secondary school were found to be smokers.³ The use of tobacco among adolescent girls is on the rise in Malaysia.³¹

In a study of villagers from Kudat, 50.0% of males and 6.8% of females used tobacco products in the past 30 days.²¹ A total of 46.6% of males were current smokers of which 15.4% were smoking more than 20 cigarettes per day and 67.9% had a pack-year cut-off of 40 and above.

Research conducted recently in Cambodia, Vietnam, and Malaysia suggests that gender norms and traditional values make it difficult for women to influence tobacco use among men.³² All of the Malaysian rural young women participants perceived that smoking was harmful to the health of the person who smoked. According to the young women, the amount of money their fathers spent on tobacco varied from as low as 5.0% to as high as 65.0% of the total household expenditure. Almost all of the female Malaysian participants were worried that the money spent on tobacco would reduce essential spending for food, health care, and education. One young woman expressed that "*spending part of the family's income on tobacco is a selfish act*".³²

Only half of the young Malaysian women who participated had tried to advise their father to smoke outside the house, typically unsuccessfully. The Malaysian fathers reported that they usually smoked anywhere and whenever they wished.³²

The main reason that men gave for not smoking inside the home was the concern that the smoke could harm their children's health, as well as pressure not to do so by their children.³² Creating a 'smoke-free home' assists in the preventing the initiation of tobacco use, promoting quit attempts and eliminating non-smokers' exposure to second-hand smoke.³² Having a mother who smokes is a strong risk factor for smoking initiation and significantly predicts ever and current smoking.³³

Socio-Economics and Smoking

The prevalence of smoking was highest among those with lower income,^{20,23,27} younger age,²³ unmarried status,^{1,21} with primary education,²³ type of occupation,²³ rural residence,²³ lifestyle (physical activity participation and nutrition label use) and health status (presence of comorbidities).²³

Smoking among Health Staff

Future physicians who smoked recorded lower levels of knowledge on smoking (4.30 ± 2.17) compared to non-smokers (5.19 ± 1.28).³⁴

In assistant environmental health officer trainees, the self-reported current smoking rate (10.8%) was much lower than among the general Malaysian population (23.1%). The smoking rate was much higher than among medical students in Malaysia and the United Kingdom.¹⁸

The prevalence of pre-clinical medical students who had ever smoked was low. In terms of patient smoking habits, most students said they would not advise their patients to quit smoking. This attitude reflects their lack of adequate knowledge and skills to promote smoking cessation among future patients.³⁵

The prevalence of overall smoking in Malaysian dentists and periodontists was 4.4%.³⁴ Most dentists and periodontists agreed that doctors, dentists, health workers and the family play an effective role in helping patients quit smoking. While 78.6% of periodontists advised all patients who smoked about smoking cessation programmes, only 34.7% of dentists did likewise.

In a study among staff of the Health Department of Melaka, the prevalence of smokers was 45.5 %, while 14.1% were ex-smokers (n = 313). Smoking was found to affect work performance, with an association between smoking status and respondent age, ethnicity, educational status, years of service and income.²⁵

Smoking Among Teachers/ University/ Public Services Staff

The prevalence of smoking among staff at a public university was found to be 10.0% (26.5% among males and 0.5% among females).²⁷ The prevalence of smoking among school teachers in Malaysia was found to be 7.8%.²⁴ Multivariate analysis showed that gender and marital status were significantly associated with smoking among school teachers.²⁴ Among the reasons given by them on the need to smoke was to relax (33.3%) followed by stress relief (28.2%).²⁴

There was a 37.6% percentage of high nicotine dependence among male civil servants which was significantly associated with the number of cigarettes and frequency of smoking daily, smoking cues (such as feeling sad and lonely, waking up in the morning and while driving), smoking rewards (feeling accepted); smoking environment at workplace and home.³⁶

Smoking among the Public

Migrant workers were classifiable as current smokers (4.2%), past smokers (5.1%) and never smokers (90.6%). Majority of migrant workers did not engage in risk behaviours such as smoking.³⁷

The prevalence of respiratory symptoms was found to be greater in current smokers among male quarry workers in Kelantan, Malaysia (tested using spirometric testing and detailed personal interviews).³⁸

A study among customers visited outdoor restaurants in Shah Alam showed peers were the main source of knowledge about harmful effect of smoking.³⁹

BEHAVIOUR AND SMOKING

Factors Associated to Smoking in Adolescents

A triad of family, environment and individual factors synergistically act to motivate adolescents toward smoking.¹ Studies among secondary and primary school students have found consistent risks and intention to smoke in the future and is associated with having family/brothers and/or and peer groups who smoke ($p < 0.001$)^{2,5,8,9,15,17,25,26,30,40-47} and poor knowledge about the ill effects of smoking,^{9,6,4,17,48} male ($p = 0.025$),^{9,40,8,13,4,45,48} age ($p = 0.037$),^{9,40,13,4,48} education level ($P < 0.001$)^{30,48} ethnicity,^{4,45,48} religion,⁴ alcohol intake,⁸ economic status,⁴ upper primary school level (standard 4, 5, 6),^{9,40} semester of study ($p = 0.025$),¹³ positive attitude toward smoking ($p < 0.001$),^{4,6,13,48} negative attitude toward tobacco control policies ($p < 0.05$),¹³ stress¹³ and the locality where respondents attended school [1.94(1.11-3.39)].^{15,41}

In a longitudinal study, a total of 14.9% of adolescents were susceptible to smoking at baseline.⁴⁹ Respondents who were identified as susceptible to smoking were 3.7 times (95% CI: 2.17- 6.30) more likely to initiate smoking compared to non-susceptible respondents after adjusting for gender, school locality, percentage of friends who smoke, paternal smoking habits, parental acceptance of smoking, and belief in the positive and negative consequences of smoking.⁴⁹ FTND revealed that 90.0% of current smokers who were lower secondary students had lower addiction to nicotine.¹⁵

Higher odds for smoking was observed for adolescents who perceived that their parents would react badly to smoking (aOR 0.84)^{2,45,118} or perceived public disapproval of smoking (aOR 0.93).^{44,120} Overestimates of the prevalence of smoking among their peers also predicted future smoking.^{50,118} Waiting for the bus (32.4%) was the most common occasion for smoking amongst secondary school students.⁴ The most prevalent risk behaviours include truancy (34.4%), loitering in public places (21.5%), bullying (14.4%), stealing (12.9%) and smoking (12.0%).⁵¹ Females and non-smoker had better knowledge of the hazards of smoking and posed more positive attitudes.⁴

Factors given by upper secondary schoolboys for continuing smoking were stress (70.0%) and addiction to nicotine (49.0%).⁴⁰ The majority of them (91.3%) were aware that cigarettes are the main risk factor for lung cancer and but only about half believed that second-hand smoking is one of the risk factor of lung cancer.^{9,52}

Among the factors that hinder smoking cessation efforts in adolescents include the environmental factors, behaviour of teenagers (personal factors), and poor self-efficacy in overcoming nicotine addiction (behavioural factors).⁵³

Factors Associated with Smoking in Adults

In adults, predictors of tobacco use include being of male gender,^{13,27,45,54,55} alcohol use, intravenous drug use,²² age,⁵⁴ income, marital status,^{16,27} ethnicity, religion,²⁷ education level,^{27,30,54,55} peer influence,³⁰ employment status,²⁷ residential area,⁵⁴ family income,²⁷ role in the family,⁵⁶ parental knowledge,⁵⁶ and health status.²³

The prevalence of ever and current smokers in Kelantan was 34% and 25.1% ($p < 0.001$).³⁰ A study carried out amongst smokers aged 60 years and above found that they had less knowledge, as well as poor attitudes and perception on the risks of smoking compared to ex-smokers and non smokers.²⁰

Studies have shown that smokers rationalise smoking as a coping mechanism that them carry on with their lives.^{13,57} About one third of smokers believe that they belonged to a light smoker category.⁵⁸ Some smokers mistakenly believe that smoking water pipes were far less harmful than smoking cigarettes, both for themselves and for those exposed to the smoke.³² Lay beliefs may prevent some smokers from quitting.⁵⁹ A comparative study reported nearly half of Malaysian smokers (49.1%) rationalised their smoking compared to Thai smokers (9.5%).⁶⁰

Branded cigarettes are often preferred by smokers in Sarawak (83.1%), with cigarettes most commonly being obtained from either friends (49.1%), or self-purchased (43.6%).⁷

Intention to Quit Smoking

The prevalence of quit attempts ranges from below 20.0% to over 50.0% across countries (Australia, Canada, China, France, Germany, Ireland, Malaysia, Mexico, Uruguay, Netherlands, New Zealand, South Korea, Thailand, UK, US).⁶¹

Only 11.3% of Malaysian smokers intended to quit within six months, whereas 20.8% of Thai smokers intended to quit.⁵ Approximately 3 out of 5 male smokers in a vocational school have considered quitting and 45.0% of them had tried at least once to stop smoking.⁵ The percentage to quit smoking among current smokers in adolescents was 61.7%.¹²

A study showed that 66.7% of current smokers (villagers in Kudat) showed no intention to quit in the next 6 months.²¹ The majority of smokers prior to the intervention were seriously planning on quitting (59.5% were at preparation stage), but over a third had no plans to quit (35.5% were at contemplation stage).⁶²

A community-based study on the prevalence and factors affecting cessation in Terengganu had recorded quit ratio of 27.0%.¹⁶ Quit rate at four months after intervention was significantly higher compared to the non-intervention group (45.0% vs. 32.0%) ($p=0.013$).⁶³

Smoking Initiation Age

In Malaysia, the mean smoking initiation age has been shown to be between 16.18 years to 18.3 years.^{17,64} The median age at smoking initiation was lower among males.²⁶ Smoking mean age among university students was 20.74 years.⁶⁴ The mean age of smoking initiation amongst secondary school students in Sarawak ranges from 12.8 years⁷ to 18.1 years.⁵⁴ In Hulu Langat, the mean smoking initiation age was between 13-15 years old (67.0%), while 21.0% of them begin smoking at below 12 years of age.⁴⁰ Half (50.0%) of all smokers from a village in Kudat started smoking before they were 18 years old.²¹ Overall mean initiation age in Terengganu for males (19.1 years) was significantly lower compared to 29.8 years for the females ($p<0.001$).

Duration of Smoking

The mean duration of smoking for the current smokers was 21.6 years (95% CI:19.1, 24).¹⁶ There was no significant difference between the mean duration of smoking between male and female current smokers ($p=0.59$).³⁰ Smoking duration of Malaysian university students was 4.41 years.⁶⁴ The overall mean duration of smoking in Kelantan was 23.9 years with a median of 23 years.³⁰ A total of 5.3% of villagers in selected Northern Borneo used chewable tobacco with median duration of 31 years.²¹

Numbers of Cigarettes Smoked

Mean number of cigarettes smoked among Malaysian adult males per day was 11.3.¹⁷ In a study comparing Malaysian and Thais in parallel, the mean cigarettes smoked per day for Malaysians averaged 13.7 while Thais smoked 13.2 sticks.⁶⁰ More than half (53.4%) of the current smokers smoked regularly (at least one cigarette daily).⁶⁵ Among those actively smoking, 96.7% smoked a lesser number of cigarettes during the fasting month.⁶⁶ Smoking frequency of Malaysian university students averaged 8.72 cigarettes per day.⁶⁴ A total of 46.6% of males (villagers in Kudat) were current smokers comprising 15.4% smoked more than 20 cigarettes per day and 67.9% got 40 pack-years and above.²¹ In another study examining health behaviours in a rural community, male smokers were found to smoke at least 5 cigarettes per day.⁶⁷ In Sarawak, one study found tobacco usage to be as high as 14 sticks per day.⁵⁴

Types of Tobacco / Nicotine Used

Electronic Cigarettes

Little is known on the use of electronic cigarettes (e-cigarettes) in Malaysia,⁵⁴ despite its popularity particularly among youths who are smokers and want to quit, children and adults who are non-smokers.⁶⁸ Awareness was higher among male, younger, more educated, and wealthier respondents. Awareness of e-cigarettes was 21.0% in Malaysia, with 3.9% of those aware being current e-cigarette users.^{69,70}

A qualitative study exploring the perspectives of vapers on the effectiveness and safety of vaping showed, at least

anecdotally, that vaping was as a method to quit smoking.⁷¹ Findings showed that vaping was used as a quit smoking aid as it not only reduced tobacco consumption but was perceived as a cheaper and healthier alternative to nicotine in the management of withdrawal symptoms.

Shisha Smoking

Shisha smoking is not adequately addressed in the current anti-tobacco policies. Shisha bars are commonly seen around educational institutions. The general public is unaware of the harmful effects of shisha smoking as it is generally assumed that shisha does not contain tobacco.⁷²

The main factor leading to the first attempt in Shisha smoking is the influence of peer pressure. Other reasons that lead them to continue smoking Shisha include the smell and flavoured taste of Shisha, easy accessibility, and the perception that it is less harmful and cheaper than smoking.⁷²

Chewable Tobacco

Females in Kudat used chewable tobacco alone, while males reported using a variety of tobacco types: factory made cigarettes (79.3%), hand rolled tobacco (37.9%), chewable tobacco (6.9%) and cigars (3.4%).²¹

Second-Hand Smoking

Avoiding second-hand smoking is seen as a main preventive measure for lung cancer.⁵² A total of 442 (55.6%) children (primary school children) lived in the presence of a household smoker.⁷⁴ Compared to other populations of similarly aged schoolchildren, Malaysian children have higher salivary cotinine concentrations.⁷⁵ Primary school students who were second-hand smokers showed no significant variation in PEFV levels ($p=0.816$).⁷⁶

Adolescents who were exposed to environmental tobacco smoke levels of >5 h/day were found to be 4 times more likely to have smoked when compared to those exposed to <1 h/day of environmental tobacco smoke.⁷⁷ Adolescents continue to be exposed to second-hand smoke in public venues in states with both comprehensive and partial-smoke-free legislations. Respiratory symptoms are common among those reporting second-hand smoke exposure on public transportation. Many venues across Malaysia seem to flout smoke-free legislation. Thus, priority should given to enforce such laws to reduce exposure.⁷⁸

In a group of housewives in a Malay community who were secondhand smokers in the privacy of their own homes, exposure to cigarette smoke was less than 10 cigarettes for less than 10 minutes per day.⁷⁹

Measures of Nicotine Dependence

Fagerstrom Test of Nicotine Dependence (FTND)

The Heaviness of Smoking Index (HSI) provides a similar prevalence rate of high nicotine dependence as the FTND⁸⁰. The prevalence in the detection of high nicotine dependence was 7.0% lower using CPD recommendations.⁸⁰ The kappa inter-rater reliability between HSI and FTND has been found to be substantial ($kappa=0.63$)⁸⁰. The sensitivity and the specificity of HSI was 69.8% and 92.5% respectively.⁸⁰

Carbon Monoxide (CO) Levels

In a study involving adult male smokers, exhaled CO proved to be a useful tool in predicting nicotine dependence.⁸¹ Exhaled CO correlated positively with FTND scores (Pearson's rho=0.398, p=0.01).⁸¹

CLINICAL FEATURES**Smoking in Association with Other Diseases***Respiratory*

School children who are exposed to cigarette smoke have an increased risk for developing cough, nasal and throat problems at night, wheezing and asthma. The risk is increased with the increasing number of smokers at home.⁷⁴

In a study involving spirometric testing of university students, it was found that the predicted FEV₁ levels had a significant inverse correlation to smoking frequency (number of cigarettes per day) (r=0.241, p=0.016).⁶⁴ FEV₁% was a predictor of the age and smoking frequency of these students (p=0.002).⁶⁴ FEV₁/FVC% was significantly associated with phlegm symptoms (p=0.03). The FEF₂₅₋₇₅% was related to age (p=0.005), height (p=0.043) and smoking duration (p=0.046).⁶⁴

Smokers who maintained abstinence were found to be less likely to develop respiratory symptoms and require hospital admission in a year compared to smokers. (OR = 4.5, CI: 1.19 -10.59; p<0.005)⁸²

Among male farmers, there was a significant reduction of acute symptoms after pesticide spraying if they did not smoke.⁸³

Tuberculosis

Combining TB treatment with tobacco cessation interventions yield better outcomes which includes better health-related quality of life (HRQoL).⁸⁴

TB patients who received an integrated intervention for six months were found to have significantly higher rates of quitting smoking when compared to those who received conventional TB treatment alone (77.5% vs. 8.7%; p < 0.001).⁸⁵

In a study related to smoking connecting TB and tobacco cessation interventions has been strongly advocated as this may yield better outcomes including better health-related quality of life (HRQoL). Participants who received the integrated intervention had a better HRQoL than those who received the usual TB care.⁸⁶

In another study, ever smokers had increased likelihood of treatment failure (OR=7.48), Defaulter rates (OR=7.17) and were less likely to be cured (OR=0.34).²² There was a significant relationship between the smoking status of a TB patient with race and initial Mantoux test.⁸⁴

Smoking was found to be a significant risk factor in the development of tuberculosis among foreign labourers.⁸⁷ Smoking behaviour was higher in females (50.5%) compared to males in this population (64.0%) (p<0.05).⁸⁷

Ever smoker TB patients have been found to be four times more likely to have slower smear conversion at two months compared to non-smoker tuberculosis patients.⁸⁴

Mortality rates among tuberculosis patients who smoke is high. Smoking has been identified as a risk factor for unfavourable outcomes among TB patients registered in DOTS programmes in terms of therapeutic compliance.⁸⁴

Oncology

Smoking is one of the factors influencing regular medical check-ups in cancer prevention besides sex and family history of cancer (p = 0.034, p=0.013, p=0.002; respectively).⁸⁸ At a tertiary care setting, smoking was associated with an increasing trend of cancer cases.⁸⁹

Breast Cancer

In a study of female breast cancer patients in Kelantan, 4.6% of the population were smokers.⁹⁰

Oral Cancer

In most Southeast Asian countries, oral cancer is caused by smoking, betel quid chewing and alcohol consumption.⁹¹ The risk of developing cancer decreases after the cessation of tobacco use. The risk of developing oral cancer in an ex-smoker is similar to an individual.⁹² There is no difference in the risk of oral cancers among smokers/tobacco users who stop smoking within ten years.⁹² It is thus important to offer effective treatment to help smokers stop smoking.⁹³

Other Cancers

In isolated cases of squamous cell carcinoma of the oesophagus, most patients (71.7%) gave a positive history of smoking.⁹⁴

Cardiovascular Disease and Diabetes

In a study which assessed the relationship between smoking and cardiovascular risk, it was found that the glycaemic index amongst males was significantly associated with smoking status (p=0.048).⁹⁵ Despite having a higher odds ratio, there was no significant association of developing diabetes mellitus between smokers and non-smokers. despite smokers having a higher odd ratio (OR=4.33; 95%CI: 0.900-20.811) (p=0.068).⁹⁵ In a univariate analysis, the duration of smoking was found to be a significant factor linked to diabetic nephropathy. This was not seen when a multivariate analysis was done.⁹⁶

In a study amongst non-ST elevation in myocardial infarction patients at a tertiary centre, the incidence of bleeding after the commencement of anticoagulants (enoxaparin) was not significantly affected by age, enoxaparin dose and duration of therapy, smoking and concomitant aspirin/ ticlopidine therapy.⁹⁷

Hypertension

Smoking 5 cigarettes was found to be significantly associated with high systolic blood pressure.⁹⁵ Conversely, smoking seemed to indicate a protective trend against systolic hypertension (OR=0.57; 95% CI: 0.266-1.230) but this finding did not achieve statistical significance (p=0.152).⁹⁵

Endocrine

There seems to be an inverse relationship between smoking and obesity.⁹⁸ A national study found the prevalence of obesity was significantly higher in a non-smoking population compared to a group of current smokers ($p < 0.001$).⁹⁸ In smaller studies which shared a parallel trend, smokers within an indigenous tribe had a lower BMI compared to non-smokers.⁹⁹ However in an adolescent population, there was no association between BMI and smoking habits.¹¹

Psychiatry

Current smokers experience a greater degree of anxiety compared to former smokers and non-smokers.¹⁰⁰ One study conducted on smokers with schizophrenia recorded higher scores in measures that reflect immediate memory, delayed recall and recognition memory than non smokers.¹⁰¹

Reproductive

Exposure to second-hand smoke during pregnancy increased the maternal risk of delivering infants with cleft lip and palate (OR=2.41, 95% CI: 1.42-4.09).¹⁰²

In assessing the effects of passive smoking in mothers, a study revealed that maternal placental and neonatal parameters did not show any difference between the exposed and non-exposed group.¹⁰³ However, placental weight showed significant correlation with maternal weight and maternal BMI in both exposed and non exposed mothers.¹⁰³ Placental weight in both Malay ($r=0.405$; $p=0.020$) and Indian ($r=0.553$; $p=0.050$) passive smokers were significantly correlated to maternal weight on admission.¹⁰³

In a study performed in 4 countries that included Malaysia, the odds ratio of erectile dysfunction amongst male smokers with no comorbidities was 2.3.¹⁰⁴

Gastroenterology

In a study evaluating the effect of smoking in peptic ulcer disease patients, there was a significant association between *Helicobacter Pylori* infection and smoking status.¹⁰⁵

Rheumatology

Two studies revealed the effects of smoking on bones and joints. The relative risk of developing hip fracture in a smoking population was 1.5 times greater for men (95% CI: 1.0 – 2.1).¹⁰⁶ Smokers were predisposed to a greater risk of developing rheumatoid arthritis when compared to never-smokers (evidenced by positive anti citrullinated protein antibody - ACPA).¹⁰⁷ There was a dose-response relationship in terms of risk of developing rheumatoid arthritis in terms of risk of developing rheumatoid arthritis through smoking.¹⁰⁷ Rheumatoid arthritis was also predominant in smokers with exposure to silica.¹⁰⁷

MANAGEMENT

Health Warnings on Cigarette Packs

Evidence shows that comprehensive warnings cigarette packaging promotes cessations.¹⁰⁸ Messages about smoking habits that affect the appearance of the smoker was found to be more effective in teenage smokers.¹⁰ However, health warning messages on cigarette packs do not appear to have

much effect on child and adolescent smokers. The failure of this intervention is attributed to the fact that the latter group is known to purchase individual cigarettes instead of buying a whole pack. In another study, the majority of children who smoked felt that displaying real pictures associated with diseases pertaining to smoking did not have any deterrent on their smoking habits.¹⁰⁹ However, they believe that the same cigarette pack warning might have the potential of creating awareness to quit smoking.¹⁰⁹

Health warning messages on cigarette packs were found to increase awareness of the risks of smoking elicit stronger behavioral responses to the warning and increase interest in quitting smoking in adults.¹¹⁰ These messages stopped smokers from having a cigarette and was an independent predictor of all phases relevant to the stages of change theory.¹¹¹ It also predicted quit intentions and self-efficacy in quitting.¹⁰ In addition, thinking about the health risks and reading the warnings added extra predictive capacity. This predictive potential was more predominant only in the early stages of contemplating change.¹¹¹ Cigarette pack warnings appeared to have a common mechanism for influencing quitting regardless of warning strength.¹¹²

Interventions

School Based

The current national tobacco control programme has been found to be ineffective in promoting smoking cessation among teenagers. This is attributed to the inadequacy of the message content, lack of exposure to the programme, and poor presentation and execution.¹¹³

There were no differences between adolescents from Malaysia and Thailand in terms of reported anti-smoking education in schools and exposure to anti-smoking messages. The provision of anti-smoking education in school was associated with a reduced susceptibility in female smoking (OR = 0.26); higher knowledge of smoking harm and higher perceived health risks were associated with reduced susceptibility of smoking among Thai females (OR = 0.53) and Malaysia male adolescents (OR = 0.63).¹¹⁴ In the same study, male students indicated the belief that print media; OR = 2.32 (95% CI: 1.31-4.10); radio; OR=1.93 (95% CI: 1.15-3.22); and the internet; OR = 1.96 (95% CI: 1.15-3.33) were very effective at delivering anti-smoking messages.¹¹³ More Thai than Malaysian adolescents received advice from their doctors and nurses about the dangers of smoking ($p > 0.001$).¹¹⁴ However, studies will assist in the development an anti-smoking program to limit smoking in universities by implementing policies against smoking.¹³

Behavioural Intervention

Group counselling is very effective in improving smokers' knowledge and quit rate, but not their attitudes toward smoking.⁶³ Factors such as the number of counselling sessions, the amount of cigarettes smoked at baseline, adherence to NRT and pre-treatment stress are important considerations for success.¹¹⁵ In an intervention which also involved counselling, higher abstinence rate was reported in intervention group (71.7%) compared to a control group (48.6%) at 6 months follow up (CO verified) (OR = 0.375; 95% CI: 0.217-0.645, $p < 0.001$).¹¹⁶

A single session of brief physician counselling has been found to be effective in improving smokers' behaviour at the workplace, but the effect was not sustained.¹¹⁷ In this study, there was a significant improvement in smoking behaviour at one-month post intervention ($p=0.024$, intention to treat analysis; OR=2.525; CI: 1.109-5.747). However, this was not significant at three-month post intervention ($p=0.946$, intention to treat analysis; OR=1.026; 95% CI: 0.486-2.168).¹¹⁷

In a study involving intensive individual and group counselling on diet, physical activity and quitting smoking among security guards of the public university showed a significant reduction in their mean total cholesterol levels and the amount of cigarettes smoked compared to the control group.¹¹⁸ A similar study showed that the worksite is an effective channel for the adoption of the new lifestyle behaviours including stopping smoking ($p<0.05$).¹¹⁹

Treatment

Nicotine-replacement therapy (NRT) was found to assist patients to quit in combination with behavioural support.^{33,120} Varenicline was reported to help to relieve craving and withdrawal symptoms among psychiatric patients.¹²¹

Quit Smoking Clinic

A total of 17.3% of smokers attending smoking cessation clinics were able to quit smoking for at least six months.¹²² At 3-month follow up, 35.4% reported abstinence.

The majority of smokers attending health clinics in Sepang, Malaysia were found to be in the 20-29 age group and were mostly males ($p<0.05$).⁴³ A total of 31.6% of attendees at a health clinic in Cheras were smokers at some point in time.¹²³ Three quarter of attendees at health clinics intended to stop smoking.⁴³ There was no significant difference noted in changes of motivation stage between relapsers and non-quitters. The same study also concluded that healthcare providers' recruitment strategies for cessation programmes should encompass smokers at all motivation stages.⁶²

The majority of dentists (98.8%) agreed that they had a potential role in smoking cessation counselling, but few of them (17.9%) were actually involved in providing the intervention. The main barriers cited were the lack of training and time in their practice.¹²⁴

A study had reported that smokers were conflicted in their beliefs and feeling about smoking and quitting.¹²⁵ Smokers who displayed greater conflict with regards to quitting were more likely to choose gradual cessation.¹²⁶ Motivation to stop smoking was found to predict cessation at 3-month follow-up.¹²⁷

Older age and longer duration of previous quit attempts have been shown to be predictors of successful quitting in the clinic population. Higher carbon monoxide reading at baseline predicted success at 6 months. Success rates varied greatly between clinics.¹²⁸

In a study which aimed to evaluate the psychometric properties of the Malay translated version of the brief questionnaire of smoking urges (QSU-Brief), the measure was found to be a suitable measure of urges to smoke.¹²⁹

Predictors of Quit Attempts/ Abstinence

Smoking fewer cigarettes per day, higher levels of self-efficacy and more immediate quit intentions were predictive of both making a quit attempt and remaining abstinent. Previous shorter quit attempts and higher health concerns about smoking were only predictive of making an attempt, whereas prior abstinence for 6 months or more and older age were associated with maintenance.^{41,122}

Smokers aged 40 years and above were 6.7 times more successful in quitting while those with high levels of confidence were nine times more likely to be successful. Self-referred smokers were ten times more successful and those attending at least 30 minutes counselling session were 12 times more successful. Those who smoked more than ten sticks per day were ten times less successful in quitting smoking.¹²²

A study which measured threshold levels of the expired-air carbon monoxide concentration reported reducing the threshold to verify claimed smoking abstinence from 10 ppm to 5 ppm made minimal difference to documented success rates. Predictors of success at quitting appeared to be unaffected by the threshold used.¹³⁰

Religion and Smoking

In a study from the International Tobacco Control Southeast Asia Survey (ITC-SEA) between Malaysia and Thailand found majority of Muslims and Buddhists from both countries believed religion discourages smoking and encouraged them to quit, but a minority cited religious reasons as a prime motivator to quit.¹³¹

Among Muslims in Malaysia, religion and not societal norms had an independent effect on quit attempts¹³² with religion often cited as a reason for not smoking.⁵ Religious belief and positive attitude towards health prevented non-smokers from smoking.⁴²

In a study among 240 Muslim men from 12 mosques in Kuala Langat, only 31.6% of smokers compared to non-smokers (87.7%) and ex-smokers (73.6%) accepted smoking as haram. They felt that it was easier to quit smoking during the fasting month of Ramadan.⁶⁶

Job Performance and Smoking

Studies showed there was no significant relationship between smoking and job performance²⁵ and psychosocial job variables with smoking cessation.¹³³ A study showed that at three months (OR=5 8.96; 95% CI: 1.14-70.76) and six months (OR=5 8.9; 95% CI: 1.15-68.65), men with higher co-worker support demonstrated a higher likelihood of quitting and those in a 'passive job' also demonstrated higher likelihood of quitting compared to those working in the 'low strain' category at six months (OR=5 9.92; 95% CI: 1.20-82.68).¹³³

The Influence of the Tobacco Industry

Many ASEAN countries still do not have well organized tobacco control strategies.¹³⁴ In Malaysia, the tobacco industry has been known to target smoking among youths despite working with the government to promote healthy youth activities.¹³⁵ Even though the government was

successful in implementing regulations such as health warnings and advertising bans, they were compromised and effectively blocked from further progress.¹³⁶ The campaign against second-hand smoking has geared tobacco companies to prepare for a major threat to their industry. These include conducting national/international symposiums, consultant 'road shows' and extensive lobbying and media activities.¹³⁷ An example of this was the flouting of the World Cup of football's no-tobacco ruling.¹³⁸

Examining the roles of the private sector in tobacco cessation programmes, it is clear that tobacco companies have manoeuvred to exploit smokers by teaming up with unwary organisations to carry out health promotions for youths.¹³⁹ The tobacco industry has repeatedly denied that they target youth through intensive marketing and advertising. However, the evidence shows that the industry has very successfully created a positive image of tobacco use among adolescents.³²

The tobacco industry must accept responsibility and compensate smokers who wish to quit. Undoubtedly private companies can gain from this affiliation. The issue which arises pertains to the means by which this promising partnership can be carried out in the most transparent manner, especially within the confines of such a highly regulated industry such as the pharmaceutical sector.¹³⁹

Total Bans of Smoking and Increased of Cigarette Tax

The main factors influencing agreement of outdoor smoking ban were marital status. Approximately 75.0% of respondents agreed to ban cigarette smoking in restaurants.³⁹

Support for total bans in air-conditioned venues was high and similar in both Malaysia and Thailand who believed there was a total ban, but self-reported compliance with bans in such venues was significantly higher in Thailand than in Malaysia (95.0% vs 51.0%; $p < 0.001$). Reporting a ban in air-conditioned venues was associated with a greater support for a ban in such venues for both countries.¹⁴⁰

Approval of total bans were more common in female medical students than in male medical students (OR =0.39 (95% CI: 0.18 – 0.86)).¹¹³ Students were the least likely to approve of total bans on cigarettes and increases in the price of cigarettes and most likely to approve bans on the use of cigarettes in public places and sales to individuals less than 16 years old.¹¹³

In Malaysia, a 10.0% increase in price would result in a 3.8% reduction in cigarette consumption over the long-run if annual tobacco tax increases were made. This reduced consumption would translate to between 174 and 179 fewer tobacco related deaths per year among the adult population. At the same time, the government would collect additional RM 437 million (US\$116 million) in cigarette excise taxes, or almost 23.0% more compared to what it would otherwise collect.³² Additional government revenues from proposed annual tax increase in Malaysia can be used to help smokers in their cessation efforts and to support tobacco farmers to switch to alternative crops.³²

Prevalence estimates of cigarette tax avoidance/evasion vary substantially between countries and across time. In Malaysia, some prevalence estimates suggests substantial cigarette tax avoidance/evasion. Important associations have been found for household income and education in the likelihood of engaging in tax avoidance/evasion. These associations however varied both in direction and magnitude across countries.¹⁴¹

Government Initiative on Tobacco Control Policy

The efficacy of current policies are influence by four main factors (a) the development of tobacco control policies due to poor law enforcement, (b) the failure of retailers to comply with the law, (c) the social availability of cigarettes to teenagers, and (d) easy availability of cheap, smuggled cigarettes.⁵³

The lacklustre nature in the enforcement of smoke-free restrictions in Malaysia is likely to contribute to our findings. There is a need to enforce existing legislation to reduce exposure in public place and at home. Importantly, the implementation of effective home smoking restriction practices are crucial.⁷⁵

Compliance with legislation appears to be particularly poor in entertainment centres and internet cafes. There is an urgent need for increased enforcement of existing legislation and consideration of more comprehensive laws to protect health.¹⁴²

Governments are required to implement varied measures to prevent smoking uptake. Health promotions only reach a limited segment of people. Hence, this results in situations where smokers are not followed-up. Treatment for tobacco is expensive and compounding to this is the high smoking prevalence burden. Many smokers are not aware of the probability of disease due to smoking. A number of healthcare providers are also not familiar with quit smoking procedures and NRT.¹³⁹

The thoughts about the harm of smoking, fear arousal, and social norms against smoking mediated the relation between TAK NAK antismoking mass media campaign on impact and quit intentions. Effective campaigns should prompt smokers to engage in both cognitive and affective processes and encourage consideration of social norms about smoking in their society.¹⁴³

Newer Modalities of Intervention

Recent intervention modalities include quitline, a web-based system services carried out by the pharmacists from the National Poison Centre through telephone. It was opened to the public in conjunction with "World No Tobacco Day" on 31st May 2005. A user must have internet connectivity. Within a period of 2 months, a total number of 58 smokers and 2 proxy callers contacted the quitline and from these 52 smokers were enrolled into the program.¹⁴⁴

Online training modules include the Certified Smoking Cessation Service Provider (CSCSP) programme, developed for practicing pharmacists to equip pharmacy students with knowledge necessary for smoking cessation counselling.¹⁴⁵

Smoking cessation intervention consisting of phone calls and counselling delivered during the first month of quit attempt revealed significantly higher abstinence rates compared to a standard care approach.¹¹⁶

Hospitals provide a good setting to implement smoking cessation intervention especially in smokers with acute and chronic medical illness.¹⁴⁶ Hospital stays also provide an opportunity for the health carer to initiate and abide by the government policy which does not allow smoking within hospitals.¹⁴⁶

Connecting TB-tobacco treatment strategies with an integrated approach may be significant among TB patients who are smokers.⁸⁵

The marketing strategies for anti-smoking campaigns in terms of the product, price, accessibility, promotions and social implications needs to be examined and weighted to ensure more effective and comprehensive programmes.¹⁰⁹

Genetic

The determinants of smoking behaviour is multifactorial. Both genetic and environmental factors play a crucial role. Research has shown that the nicotinic acetylcholine receptors (nAChRs) influences nicotine addiction among smokers. The α -4 subunit of nicotinic acetylcholine receptor (CHRNA4) gene is associated with smoking behaviour in many populations. In a recent study in a Malaysian population, AA genotype frequency for CHRNA4 rs2236196 polymorphism in the smoker group was 80.6% while it was 77.0% in non-smokers. No mutation (GG genotype) was detected in both groups.¹⁴⁷

Recommendation

There is a need to implement more comprehensive smoke-free legislation nationally across Malaysia.⁷⁷ A national policy on tobacco control which enables an integrated, inter-ministerial approach is vital.¹³⁶

Preventing adolescents from becoming smokers is the key to reducing national prevalence rates in smoking.⁷⁷ Strategies should be undertaken to equip students with skills of dealing with stressful situations and instill healthy lifestyle ideals.¹⁴ Knowledge of smoking hazards should be included in the education programme to reduce initiation of smoking among adolescents.⁶ Continuous and more comprehensive anti-smoking policy measures are needed in order to further prevent the increasing prevalence of smoking among Malaysian men, particularly those who are younger, of Malay ethnicity,^{17,23} lower education, those residing in rural residential areas and with lower socio-economic status.¹⁷

Early intervention on smoking prevention and risk awareness is perhaps more effective if initiated before the age of 12 years.⁷ Smoking prevention programmes should begin early in primary schools.⁴⁰ Existing anti-smoking programmes need to take into account the factors that promote smoking to reduce the prevalence of intention to initiate smoking and increase the intention to cease smoking among adolescents.¹² Adolescents should be educated on effective coping strategies in managing stress and learning to be assertive.⁴⁰ It is vital to

address the perceptions of social norms⁴⁴ via intervention programmes to correct the misperception of peer smoking.⁵⁰ The majority of Malaysians agree that laws should be created for smokers with children but admitted to not setting a good example to their children as they reported smoking openly in front of them.¹⁰⁹

National efforts to prohibit smoking in private spaces such as homes and cars need to be enhanced. Knowledge is significantly associated with appropriate practice towards secondary smoking. More efforts should refocused to increase and disseminate knowledge of the harmful effects of second-hand smoking.⁷⁹ In view of the significant health risks posed to children by second-hand smoke, public health policies are needed to protect this vulnerable population. The aim of such policies is to ensure the right of every child to grow up in an environment free of tobacco smoke.⁷⁴

Intensification of health education and anti-smoking programmes and modification of external factors in early adolescence are recommended to prevent smoking initiation.²⁶ Measures such as the teaching of skills to resist social pressure to smoke, the establishment of peer support groups and involvement of parents in anti-smoking programs are recommended among lower secondary school students.¹⁵ Susceptibility measure is a reliable predictor (in adolescents) and can be used as a screening tool to identify adolescents who are at risk of initiating smoking.⁴⁹

In view of these matters, the Ministry of Health Malaysia is thus recommended to immediately design more national health enhancement programmes to highlight and promote the importance and benefits of living a healthy lifestyle. Ideally, multi-lingual media can be used as the channel to deliver these messages^{23,109} including on public transportation.¹⁰⁹ Anti-smoking programmes with an emphasis on educating and providing support for smoking cessation should be integrated in the health care policy for the elderly.²⁰ Strategies aimed at correcting the belief that smoking can reduce weight should be included as one of the components in the prevention of smoking.¹¹ Quit smoking interventions should be emphasized and be carried out on a larger scale during the fasting months.⁶⁶ Smoking cessation strategies should be tailored according to the different smoking stages.⁴⁵

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

The following research reviewed carries relevance for programmes targeted at smoking cessation in the current population. Identification of risk and protective factors can help inform quit smoking strategies.

Epidemiological data derived from this review suggest the need for a targeted intervention programme in the community. The cornerstone of a 'smoke-free' society relies on the capacity to perform targeted screening on susceptible groups within the community. Both public health officials and primary care clinicians should collaborate in identifying specific segments of the population that require preventive measures.

As evidenced in this review, the criteria of screening interventions should include, among others, different age groups (adolescents/mean initiation age), gender groups (males), specific populations (adolescents, schoolchildren, working class) and selective regions in the country (FELDA settlements). Subsequently, primary care clinics can play an instrumental role in providing further care for these vulnerable groups through readily available programmes such as smoking cessation clinics.

Smoking clearly leads to serious health hazards in the society. Increased efforts in smoking cessation measures could help decrease the burden of various health problems in the country. Thus, health problems in patients should prompt clinicians to make a conscious effort to inquire about their smoking habits.

With the lack of local long term outcome studies, the role of e-cigarettes, vaping and shisha smoking remains an area of controversy. At present, as seen amongst shisha smokers, there is a widespread belief that these 'safe' alternatives to smoking (devoid of tobacco) are less harmful than cigarette smoking. In the absence of concrete information on the safety of these smoking habits, it would be prudent to strictly regulate the consumption of vaping and shisha smoking. Healthcare providers should be tasked to educate the public and enable them to make an informed decision with regards to these newer smoking alternatives. This preemptive measure could help avoid the creation of a 'hidden reservoir' of health burden in the future.

SECTION 3: FUTURE RESEARCH DIRECTION

Numerous constraints impede the progress of research into smoking cessation in Malaysia, chiefly a lack of resources such as funding, manpower, and waning interest in an area that has received widespread attention at an international level.

Most studies in this area are saturated with prevalence studies targeting adolescents and factors associated with smoking initiation. The overemphasis on student initiated research into this area has resulted in research samples largely from school and institutional settings. Immediately lacking are studies examining smoking in adults and special groups. We need to develop more extensive collaborations between centers to overcome limited resources within a single centre when designing future studies in this area.

There is also the constraint of recruiting new samples at quit smoking clinics due to various reasons such as smokers themselves not seeking clinic help to quit smoking and healthcare workers not doing enough to encourage participation. Community intervention programmes are sorely needed for smokers who want to quit without clinic assistance.

At present there are few clinical trials, pharmacotherapy and behavioural support interventions available to improve cessation. There is a need for more clinical trial research. To date, there has been no research done examining the side effects of varenicline or any other treatment methods in

Malaysia. A safety profile of all drug based smoking cessation interventions would inform both users and prescribers.

Research into the relationship among environmental factors, behavioural, developmental, social and other factors in greater depth and in relation to interventional studies is required to determine new interventional strategies for quitting smoking.

There is a need for conclusive research into the use of e-cigarettes and vaping and its role in helping smokers quit smoking. There is currently a lack of local data as to whether electronic cigarettes may be a gateway into conventional tobacco smoking for never smokers by increasing the initiation of smoking in adolescents and young adults. We do not know much if electronic cigarettes can assist recalcitrant smokers to quit in Malaysia. There is an urgent need of scientific evidence in using electronic cigarettes as a 'tobacco control strategy' without additional rigorous studies. The consequences of the recent move by the government to prohibit and confiscate vape juices containing nicotine should also be examined. Long term studies examining the health effects of vape usage should be undertaken, along with sourcing treatment to help vapers quit.

It would be interesting to determine the consequences of the recent 40.0% price hike for cigarettes, which may possibly result in higher use of contraband cigarettes, an increase in the number of e-cigarettes users, or a higher number of individuals quitting smoking altogether.

There is a need to review and enhance the existing mandatory health warning messages on cigarette packs in Malaysia and the implementation of plain packaging in Malaysia.

Lastly, for Malaysia to achieve 'tobacco-free' nation status by 2045 research in areas to strengthen tobacco control enforcement and legislation, community empowerment through multi-multi-sectorial and inter-agency collaboration and MPOWER strategies are setting the future direction of the research in this country.

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A Review of Coronary Artery Disease Research in Malaysia

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ABSTRACT

Coronary artery disease is the major cause of mortality and morbidity in Malaysia and worldwide. This paper reviews all research and publications on coronary artery disease in Malaysia published between 2000-2015. 508 papers were identified of which 146 papers were selected and reviewed on the basis of their relevance. The epidemiology, etiology, risk factors, prevention, assessment, treatment, and outcomes of coronary artery disease in the country are reviewed and summarized. The clinical relevance of the studies done in the country are discussed along with recommendations for future research.

KEY WORDS:

Acute coronary syndrome, myocardial infarction, coronary disease, coronary artery disease, ischaemic heart disease

INTRODUCTION

Coronary artery disease is the leading cause of mortality worldwide and in Malaysia.¹ Amongst the more developed countries, the highest death rates from coronary heart disease are in the Ukraine and Russian Federation with 718 and 654 deaths per 100,000 population respectively, while the lowest are in South Korea and Japan with 36.5 and 47.0 deaths per 100,000 respectively.² Although much research has been done on coronary artery disease worldwide, it is important to review the research done in Malaysia to better understand the disease in the country and how this impacts on clinical practice locally.

This paper reviews all papers published on coronary artery disease (CAD) research done in Malaysia between 2000 and 2015. A literature search of all papers published on coronary artery disease in Malaysia was done as previously described.³ The PubMed search involved the following medical subject headings (MeSH): acute coronary syndrome, myocardial infarction, coronary disease, and coronary artery disease. 508 articles were found of which 146 were included in this review based on their relevance.

SECTION 1 – REVIEW OF THE LITERATURE

ETIOLOGY

The etiology of coronary artery disease involving atherosclerosis is well studied. A fundamental role for

inflammation in atherogenesis has been recently demonstrated. Tiong *et al*⁴ examined the role of early inflammatory markers namely interleukin-6 (IL-6), von Willebrand Factor (vWF) and platelet activation marker, P-selectin, in the early phases of acute coronary syndrome (ACS). The authors measured serum levels of these markers in 22 ACS patients and 28 stable CAD controls. They found a significant increase in serum levels of IL-6 and vWF in the ACS group compared to controls. This is consistent with studies showing a prominent role of inflammation and endothelial dysfunction in the early phase of ACS. In another study, Tiong *et al*⁵ demonstrated that serum and peripheral blood levels of CRP and vWF were significantly higher in ACS reflecting an acute phase response due to endothelial dysfunction in early the phase of ACS.

EPIDEMIOLOGY

According to the World Health Organization, CAD accounted for 98.9 deaths per 100,000 population in Malaysia in 2012, or 29,400 deaths (20.1% of all deaths); it is the most common cause of deaths in the country.¹ The Malaysian burden of disease study⁶ conducted in 2000 found CAD to be the biggest cause of death with a total of 22,158 deaths or about one fifth of all deaths. Much information on the burden of disease has also been obtained from death certifications and hospital admission records in Ministry of Health hospitals where circulatory disease accounted for 6.99% of total hospital admissions and 23.34% of all hospital deaths in 2014 (*KKM Health Facts 2015*).

The National Cardiovascular Disease database (NCVD) is another important source of information on the epidemiology of CAD in Malaysia. It provides useful data from 15 public hospitals, 1 university hospital and the National Heart Institute. The acute coronary syndrome (ACS) registry enrolls patients presenting with acute coronary syndrome, ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (UA), prospectively, while the percutaneous coronary intervention (PCI) registry enrolls patients undergoing PCI in participatory sites.

Age

The NCVD-ACS registry showed that Malaysians are having ACS at a younger age compared to the developed countries, with a mean age of between 55.9 to 59.1 years compared to

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mean ages of between 63.4 to 68 years in most developed countries.⁷ Muda and colleagues⁸ retrospectively reviewed the medical records of 165 patients in Hospital Universiti Sains Malaysia with angiographically proven CAD from 2002 to 2004 and found 92 patients (55%) had premature CAD (men less than 55 years old and women less than 65 years). These cases are associated with a positive family history of heart disease and low HDL levels.

More recently, Zuhdi *et al*⁹ looked into the NCVD-PCI registry data between 2007 to 2009 and categorized the patients into young (less than 45 years for men, and less than 55 years for women) and old (45 years and older for men, and 55 years and older for women). There were 1,595 patients of which 16% were categorized into the young CAD group and were significantly associated with more active smoking and obesity compared to the older group. The study also found a preponderance towards single vessel disease in the young CAD group with better clinical outcomes.

Gender

CAD generally affects men more than women. Lee *et al*¹⁰ studied the various aspects of gender differences in 10,554 PCI patients in the NCVD-PCI registry between 2007 to 2009. Women on average were 5 years older than men at presentation and with higher prevalence of risk factors. The in-hospital and six month mortality were also higher in women. In another paper, Lu *et al*¹¹ looked into the differences in gender in the NCVD-ACS registry from 2006 to 2010 and found that among 13,591 patients, 24.2% were women and they had more risk factors, were unlikely to undergo intervention, and had higher mortality.

Idris *et al*¹² studied the NCVD-ACS registry patients between 2006 and 2008 specifically on woman of reproductive age. The authors reported that out of 9,702 patients, 24.2% were females but only 1.9% were at the reproductive age (from 20 to less than 40 years of age) and was associated with Indian ethnicity, diabetes mellitus and hypertension. Young female patients commonly present with STEMI and have poorer prognosis.

Murty *et al*¹³ reviewed 5,579 autopsy reports done at University Malaya Medical Centre from 1996 to 2005 to study the prevalence of cardiac deaths in females and found 83 out of 936 female deaths were due to cardiac causes. The three main causes reported in the study were advanced CAD (14.5%), hypertensive heart disease (13.3%) and coronary atherosclerosis (12.0%). The study reported that hypertension, diabetes and pre-menopausal age were the most significantly associated factors.

Ethnicity

Malaysia is a multi-racial country whereby 67.4% are Malays, 24.6% Chinese, 7.3% Indians and 0.7% others. Lu and colleagues⁷ examined the ethnic differences in the NCVD-ACS registry between 2006-2010. Indians were over represented in comparison to the general proportion of ethnicities. In terms of risk factor differences, Malays had higher body mass index (BMI), Chinese had higher prevalence of hypertension and hyperlipidemia, while Indians had higher rates of diabetes mellitus and family

history of premature CAD. Chiam *et al*¹⁴ studied the prevalence of ethnicity and conventional risk factors of diabetes mellitus, hypertension and hyperlipidemia in 302 patients who were admitted for CABG in their centre. Indian patients were associated with a combination of all three risk factors while the Chinese and Malays were mostly associated with hypertension and hyperlipidaemia.

Dhanjal *et al*¹⁵ compared the cardiovascular risk factors profile of Asian patients admitted with myocardial infarction in a hospital in Kuala Lumpur (42 patients) and in Birmingham, U.K., (28 patients), with Caucasian patients admitted with myocardial infarction in Birmingham (20 patients). The study found a higher prevalence of diabetes amongst Asians in both countries compared to Caucasians which may explain the higher prevalence of CAD in this ethnic group regardless of locality.

RISK FACTORS

Much is known about the risk factors for coronary artery disease and its prevalence amongst the population in Malaysia. According to the World Health Organization, 11.6% of adults in the country have raised blood glucose, 28.8% have raised blood pressure, 10.4% are obese, and 43% of adult males are smokers.¹ Much information has also been obtained from the National Health and Morbidity Survey (NHMS), a national household survey of Malaysians. The NHMS is carried out at 4 yearly intervals (4th NHMS in 2011). It is a population-based, cross-sectional epidemiological study using two stage stratified method of sampling. It provides useful and valid data on the prevalence of risk factors for non-communicable diseases (NCD). In the NHMS 2011¹⁶, 18,231 adults aged 18 years and above were recruited. 32.7% were found to be hypertensive, two thirds of whom were newly diagnosed. The prevalence of diabetes was 15.2%, with more than half of them newly diagnosed. 35.1% had hypercholesterolemia (serum total cholesterol >5.2 mmol/L). The high prevalence of coronary artery disease risk factors hypertension, diabetes mellitus, dyslipidaemia, smoking and obesity are also consistently reported in the NCVD database registry which publishes annual reports. The NCVD-ACS17 annual reports consistently report more than 95% of patients having at least one established cardiovascular risk factor on admission for ACS.

Table I summarizes the studies on coronary artery disease risk factors prevalence in the country. Most of the studies were done in urban populations with specialist cardiology services. In a case-control study done by Suleiman and colleagues¹⁸ in Hospital Kuala Lumpur, out of 102 patients who were admitted to the male medical ward, 44 were diagnosed as CAD and 58 with other diagnosis. Smoking and hypercholesterolemia were significant predictors of CAD diagnosis in this study. In another study, Ahmad and colleagues¹⁹ enrolled 525 patients with unstable angina or NSTEMI in 17 tertiary hospitals between 2004-2005 and found 96.8% with at least one established risk factor. Of the 525 patients, 66.1% of patients had hypertension, 38.9% diabetes mellitus and 40.4% dyslipidaemia, consistent with the NCVD-ACS findings. In another study, Chiam *et al*¹⁴ retrospectively reviewed the risk factor prevalence in 302

CABG patients. The study found that the prevalence of diabetes mellitus, hypertension and hyperlipidaemia was 45.7%, 78.8% and 89.1% respectively. Indians had the highest propensity of having all the three risk factors while Chinese and Malays most frequently presented with the combination of hypertension and hyperlipidaemia.

There are a few studies on risk factors prevalence in the rural population. Nawawi *et al*²⁰ collected data on the prevalence of CAD risk factors in rural Pahang from 1997-1999. The study recruited 609 subjects and found that the prevalence of CAD risk factors was comparable to that in the urban population: dyslipidemia (67.3%), hypertension (30.3%), smoking (24.4%), diabetes (6.4%), impaired fasting glucose (13.9%), overweight/obesity (44.7%) and increased waist-to-hip ratio (48.5%). Similarly, Yunus and colleagues²¹ studied the prevalence of hypertension and smoking in rural Selangor, and found high prevalences of risk factors: 28.6% hypertensive and 21.1% smokers. However, a study by Chang *et al*²² in rural Sarawak found lower prevalence of risk factors: 13.5% hypertension, 1.5% diabetes, 15.4% smokers and 22.6% hypercholesterolemia.

Hypercholesterolemia

Hypercholesterolemia is an established risk factor for CAD. Khoo *et al*²⁴ reviewed the patterns of lipid profiles and CAD prevalence in Asia. The authors found that less developed countries had lower levels of serum lipids and ultimately lower CAD prevalence. Serum total cholesterol and therefore CAD rates can be expected to increase as developing countries progress.

Rafidah and colleagues studied the relationship between blood pressure variability (BPV), arterial compliance and hyperlipidemia²³. Defining hyperlipidemia using TG:HDL ratio, 22 hyperlipidemia patients and 22 normolipidaemia controls were included. There was a significantly higher BPV in the hyperlipidaemic group as compared to the control group but no significant difference in terms of arterial compliance between the two groups.

Familial Hypercholesterolemia

Khoo and colleagues²⁵ reported an extensive genetic study on familial hypercholesterolaemia (FH). They studied the genetic mutations of 86 unrelated FH patients and found 23 having LDL receptor gene mutations but none had the APO B-3500 mutation which is commonly reported in the literature. This might explain the lower LDL level and rarer premature coronary events in Asian FH patients. Azian *et al*²⁶ reported their DNA mutation screening technique for 72 FH patients in which four different mutations in the LDL receptor gene were detected and again no APO B100 gene mutation was found. Al Khateeb *et al*²⁷ screened 154 unrelated FH patients in Kelantan and found a total of 29 gene sequence variants with 8 of the variants reported for the first time in the literature.

Khoo *et al*²⁸ reported two different paediatric FH cases to highlight the unique presentation and discussed the management. Junit *et al*²⁹ published a case report of the first A519T mutation found in an Asian FH patient.

Metabolic Syndrome

Yeow *et al*³⁰ recruited 4,341 subjects to study the prevalence of metabolic syndrome and its association to CAD risk (using cardiovascular risk markers of high-sensitivity C-reactive protein, microalbuminuria and HbA1c). They found the prevalence of metabolic syndrome in our population to be high (42.5%) with a significantly higher HbA1c, LDL, albumin:creatinine ratio, and high-sensitivity C-reactive protein levels, putting them at higher risk of CAD.

Homocysteine

Homocysteine has been associated with cardiovascular diseases but many studies looking into the causality of this relationship have yielded conflicting results. Azizi *et al*³¹ studied the relationship between total plasma homocysteine levels (tHcy) and components of metabolic syndrome and risk factors for CAD (fasting plasma insulin, glucose level, fasting lipid profile). They recruited 44 hypertensive subjects and found only insulin levels to be inversely correlated with homocysteine levels, and no good evidence to associate CAD risk to homocysteine levels.

Choo *et al*³² examined the role of gene polymorphism in 5,10-methylenetetrahydrofolate reductase (MTHFR) in the metabolism of folate, B vitamins and homocysteine. The authors recruited 100 subjects and took their folate, B vitamins, and homocysteine levels to detect the presence of MTHFR gene polymorphism. They found folate, vitamin B12 and B6 levels were highest in the wild genotype in all ethnic groups, and subjects with heterozygous and homozygous genotypes showed the highest homocysteine levels. Gene polymorphism was commonest in Chinese and it influenced the folate and homocysteine metabolism.

Peripheral vascular disease and abdominal aortic aneurysm

Leong *et al*³³ studied the prevalence of peripheral artery disease (PAD) and abdominal aortic aneurysm (AAA) in CAD patients. The authors recruited 102 patients who were admitted for ACS and found a high prevalence (24.5%) of patients fulfilled the diagnostic criteria of PAD but a low prevalence (2%) of AAA. Most (68.0%) of patients with a diagnosis of PAD were asymptomatic; two factors were significantly associated with PAD namely smoking and age more than 60 years.

Genetic profiling

The role of ethnicity and family history in CAD suggest that genetic predisposition is an important risk factor. Abdullah *et al*³⁴ studied the global gene expression profile of the peripheral blood in CAD patients to look for potential causative gene candidates in our population. The authors analyzed the gene expression of a group of 12 CAD patients (angiographically more than 50% stenosis) and 11 controls, and were able to identify many genetic variants featured prominently in the CAD group. 18 of them were previously known to be involved in CAD and a further 137 new gene variants were identified with no known function.

Normaznah *et al*³⁵ studied the -344T/C polymorphism of CYP11B2 gene for an association with CAD. The study sampled bloods from 79 patients with angiographically

diagnosed CAD and 84 healthy controls and determined the allele and genotype frequencies of the CYP11B2 gene in them. They found no significant difference between -344T/C polymorphism of CYP11B2 gene in the two groups.

Chu *et al*³⁶ studied the relationship between genetic polymorphism of cholesteryl ester transfer protein (CETP) and endothelial nitric oxide synthase (eNOS) and the risk of CAD. They recruited 237 patients with CAD and 101 as controls and sampled their genotype. The study found a significant difference in the CAD group with higher frequency of concomitant presence of both CETP B1 and eNOS 4a alleles in Malays and Indians but not in Chinese.

Chlamydomphila pneumonia

Chronic infection of *Chlamydomphila pneumonia* had been implicated in the development of atherosclerosis. Naidu *et al*³⁷ examined the ethnic distribution of *C.Pneumonia* antibodies in our population and a possible correlation with coronary artery disease. They measured the antibody titre in 110 CAD patients and 158 healthy controls. They found Indians had the highest seropositivity (58%) and this was even more evident in the CAD group (Indian positive in 65%, with higher titre). The difference of *C.Pneumonia* seropositivity between the two groups was statistically significant and may explain the higher CAD prevalence among the Indians.

Psychological factors

The association between psychological illnesses and CAD is explained through numerous mechanisms such as higher prevalence of smoking, alcohol intake and sedentary lifestyles. Sidik *et al*³⁸ studied prevalence of depression among the elderly in a rural area and found that depression was closely associated with CAD, with 9% of elderly with chronic illnesses especially CAD having depression; 5.6% were depressed without chronic illnesses. In another prospective study conducted by Michael *et al*³⁹ in 65 ACS patients, those with depression were ten times more likely to have recurrence of cardiac events. In another study on Type D personality (the distressed personality), Satpal *et al*⁴⁰ validated the Malay version of Type D Personality Scale (DS14) before recruiting 195 CAD patients to determine the prevalence of Type D personality among them. They found 28.2% of the patients with CAD were of Type D personality.

Occupation

Several studies were done on specific occupations. Norazmi *et al*⁴¹ recruited 176 fishermen and found a very high 76.5% prevalence of smoking. Also, fishermen in general were at high risk of CAD as 91.7% of them had one or more CAD risk factors. In another study, 130 security guards were enrolled by Lua *et al*⁴² and had their risk of CAD stratified. 53% of them were at very high CAD risk according to the Personal Risk Chart. The majority of them had hypercholesterolemia (74.8%) and high BMI (47.8% overweight, 14.8% obese); these may due to unhealthy diet, nature of their job and social class. Separately, Nazri and colleagues⁴³ investigated the prevalence of hypertension in shift work factory workers. The authors recruited 76 shift workers and 72 day workers and found higher prevalence of hypertension in the shift workers (22.4%) compared to day workers (4.2%).

Studies on other possible risk factors

Non alcoholic fatty liver disease

Chan *et al*⁴⁴ recruited 399 diabetic patients to investigate the association between ultrasonography-diagnosed non-alcoholic fatty liver disease (NAFLD) and CAD. The authors found 49.6% of the patients fulfilled the diagnostic criteria of NAFLD on trans-abdominal liver ultrasound but only 26.6% of patients had evidence of CAD based on history, ECG findings and previous medical record review. They found no statistical association between NAFLD and CAD in diabetic patients.

Microalbuminuria

Some studies in the West found microalbuminuria to be associated with CAD. Yeo *et al*⁴⁵ studied the association of microalbuminuria in diabetic patients and CAD risk (marked by blood sample for highly sensitive C-Reactive Protein (hsCRP), fibrinogen and lipoprotein A levels). The authors recruited a total of 107 patients with and without microalbuminuria and found no significant difference in the levels of all the CAD predictors between the two groups.

Rheumatoid arthritis

Patients with rheumatoid arthritis (RA) have been reported to have increased risk of cardiovascular events compared to the normal population. Ma *et al*⁴⁶ conducted a pilot study primarily to compare the prevalence of subclinical CAD using CT angiography in 47 RA patients in remission and 47 non-RA patients with atypical chest pain as controls. CT angiography showed evidence of CAD in nine (19.1%) RA patients and three (6.4%) controls. There was no significant association between CAD and RA in this pilot study.

ABO blood group

Sheikh *et al*⁴⁷ investigated the association between blood group B and myocardial infarction. The authors recruited 170 patients with diagnosis of myocardial infarction and another group of healthy controls. The study found 31.8% of the MI patients were blood group B and 30% of the controls were blood group B. Logistic regression showed no significance to suggest any association between blood group B and myocardial infarction.

Case Reports

There were a few case reports on rare causes of coronary artery disease. These are usually CAD cases in young patients with no common risk factors. Azarisman and colleagues⁴⁸ reported two cases of STEMI secondary to commencement on appetite suppressant phentermine and sibutramine. Ngow *et al*⁴⁹ described an extensive STEMI due to congenital anomaly of myocardial bridging and Oteh *et al*⁵⁰ reported another case of congenital anomaly of severe LAD stenosis with proximal arteriovenous malformation. Muthupalaniappen and colleagues⁵¹ described a very rare case of STEMI at the age of 15 years, with aneurysmal dilatation and tortuous LAD on angiogram. Jasmin *et al*⁵² encountered a case of infarcted myocardium due to vasospasm in a 13 year old systemic lupus erythematosus patient. Liew *et al*⁵³ reported a case of recurrent coronary artery spasm simulating inferior myocardial infarction who was previously stented. Sulaiman and colleagues⁵⁴ described a case of eosinophilic granulomatosis with polyangiitis (Churg Strauss Syndrome)

who presented uncommonly with acute myocardial infarction first before other more suggestive symptoms such as asthma, skin manifestations and peripheral neuropathy. Wahab *et al*⁵⁵ reported their experience in using alpha-blockade in an inotropic-dependent hypotensive pheochromocytoma patient secondary to myocardial infarction.

ASSESSMENT

Cardiac assessment of the patient with known or suspected CAD are performed both in the acute setting to diagnose acute coronary syndromes and in the chronic stable patient to diagnose CAD and evaluate the need for coronary artery revascularization. Several research studies were done to evaluate and improve on the existing cardiac assessment and investigation tools, and also some new ones.

Risk prediction

Prediction of cardiovascular diseases using scoring systems based on risk factors is useful in patients presenting with symptoms suggestive of CAD to help guide appropriate investigations and treatment. It is also useful in primary preventive treatment of CAD. More recently, it has also been evaluated for the diagnosis of acute coronary syndromes.

Chia *et al*⁵⁶ conducted a validation study on the Pooled Cohort Risk Equation, a scoring system used to estimate the 10-year primary risk of atherosclerotic cardiovascular disease (ASCVD) among patients without pre-existing cardiovascular disease who were between 40-79 years of age. The following parameters are used in the scoring system: gender, age, race, total cholesterol, HDL cholesterol, systolic blood pressure, receiving treatment for high blood pressure, diabetes, and smoking status. The authors reviewed 922 patients' clinical records at baseline and subsequent ASCVD events over 10 years. The study found that the Pooled Cohort Risk Equation score overestimated ASCVD risk; there were less ASCVD events than predicted. However, these observations are retrospective; primary prevention treatment had been instituted in many of the patients and is likely to have influenced the results.

The Rose screening questionnaire (RQ) has been used to detect angina pectoris for epidemiological surveys since 1962. Hassan *et al*⁵⁷ translated the RQ into Bahasa Malaysia and adapted it cross-culturally. The translated Malay version of RQ was shown to have a good inter-rater and intra-rater reliability.

Metabolomics study profile changes in small molecules associated with diseases. Incorporating metabolomics into a prediction model was studied by Muhamed *et al*⁵⁸ to predict CAD risk in Orang Asli. The authors recruited 31 urban patients with myocardial infarction and 23 urban healthy controls to compare the metabolite expressions and form a prediction model. Out of 34 Orang Asli tested using the prediction model, 7 were clustered into the higher risk group. Separate biochemistry tests in these 7 subjects found abnormalities in their lipid profile. The authors suggest this as a useful diagnostic alternative for CAD as compared to the current diagnostic methods.

Bulgiba and colleagues⁵⁹ conducted a study on the accuracy of a prediction model using signs and symptoms in diagnosing acute myocardial infarction (AMI). The authors studied 887 patients and found 69 possible variables that could be predictive. 9 variables were significant on multiple logistic regression. The degree of accuracy of this model was 80.5%. The authors concluded the study with a suggestion to incorporate the model with an artificial intelligence method to increase the predictive accuracy. Following that, in a separate paper, Bulgiba and colleagues⁶⁰ incorporated the artificial neural networks (ANN) method in the model. ANN is an artificial intelligence method that arithmetically computes an output from a list of inputs. The results showed that ANN can perform as well as multiple logistic regression models even when using just a selection of 9 clinical symptoms as inputs. The superiority of ANN method was also reported by Purwanto *et al*⁶¹ in his study with data collected from 929 patients to construct prediction models. Aion *et al*⁶² and Lahsasna *et al*⁶³ concurred with the accuracy of ANN in prediction accuracy.

Electrocardiogram

The electrocardiogram (ECG) is the most readily available and immediate tool to diagnose acute coronary syndromes and myocardial infarctions (MI). Gupta *et al*⁶⁴ recruited 125 patients who were admitted as suspected MI using ECG and cardiac enzyme levels (creatinine kinase-MB and troponin T) at presentation and evaluated the incidence of "false alarm" by capturing the final diagnosis on discharge. The study found revision of the diagnosis in 48 patients (38.4%). The sensitivity and specificity of the initial ECG changes were 54.5% and 70.8%, respectively while raised cardiac enzymes had a sensitivity of 44.3% and specificity of 95.8%. The authors concluded that a significant proportion of patients in Malaysia are admitted with a false alarm, and the efficacy of the ECG was comparable to the West, but cardiac enzymes had a much lower sensitivity.

Exercise stress ECG

The exercise ECG is an appropriate first line investigation of patients presenting with symptoms suggestive of angina. Ng *et al*⁶⁵ reviewed the benefits of open access exercise stress ECG whereby these were ordered and conducted by the primary care physicians. In 145 tests done, 80.7% was indicated for chest pain. Only 22.1% was found to be positive, 52.8% were negative, 18.1% and 6.9% were uninterpretable and inconclusive respectively. The authors concluded that most of the stress tests had no conclusive diagnosis and most were ordered to rule out CAD in chest pain rather than to diagnose it.

Biomarkers

An increased cardiac troponin I or T (cTnI or cTnT) level is defined as a measurement above the 99th percentile concentration of a reference population. Sthaneshwar *et al*⁶⁶ established the 99th percentile concentration in our population using ADVIA TnI-Ultra method in 234 healthy men and 208 women. The authors also found no significant difference of cardiac troponin levels between gender and among different ethnic groups. The 99th percentile for ADVIA TnI-Ultra is 0.061 microg/L and a single cut-off value based on this 99th percentile can be used in our population for diagnostic purpose.

Newer biomarkers

Diabetics are at increased risk of atherosclerosis. Pathogenesis may involve increased production of advanced glycation end products such as N ϵ -(carboxymethyl) lysine (CML) due to hyperglycaemia. Ahmed *et al*⁶⁷ compared the levels of CML in 60 diabetic patients with CAD, 43 diabetic patients without CAD and 80 matching healthy controls. The authors found significantly higher CML levels in the diabetics and CAD group compared to the diabetic but non CAD group. This suggests a promising role of CML levels as a biomarker to detect development of IHD in diabetic patients.

The levels of most blood biomarkers are usually obtained from the peripheral circulation. Fong *et al*⁶⁸ studied the levels of C-reactive protein (CRP), myeloperoxidase (MPO), soluble CD40 ligand and placental growth factor (PGF) in both coronary circulation and peripheral circulation among ACS and stable CAD patients. Recruiting 39 ACS patients and 40 stable CAD controls, the authors sampled coronary bloods from occluded coronary arteries during angiogram as well as the peripheral venous blood for comparison. The levels of all the markers was significantly increased in ACS group in both the peripheral and coronary circulation. These markers are potentially useful for the accurate diagnosis of ACS. Interestingly, the level of PGF in coronary blood is much higher than in the systemic circulation suggesting that PGF may be released from the culprit site.

Samsudin and colleagues⁶⁹ looked into the usage of Copeptin, a surrogate marker for vasopressin as a combination biomarker with routine troponin. Copeptin increases immediately following an AMI in several studies, and when used in combination with troponin at presentation with AMI, was able to rule out AMI much earlier and with a high negative predictive value. It has diagnostic, prognostic and risk stratifications values but the cost effectiveness of introducing an additional biomarker needs to be determined.

Red cell distribution width (RDW) is a measurement of the variation of red blood cell (RBC) size. It has been suggested that the structural change in RBC of diabetic patients impairs their function and can lead to thrombosis. Ismail and colleagues⁷⁰ assessed the association between RDW and CAD by recruiting 472 diabetic patients admitted for coronary angiogram. Defining CAD as significant stenosis of more than 50% in a coronary artery, the authors found no RDW level difference between the CAD and non-CAD group to suggest an association.

Echocardiography

Echocardiography, particularly stress echocardiography, is a useful investigation in patients at intermediate or high risk of CAD. However, interpretation of the acquired images is subjective and depends on the acoustic windows. Acharya *et al*⁷¹ studied various grayscale features of echocardiography images from a database of 400 CAD cases and 400 normals, and compiled all the features that had good discriminating capability into a Gaussian mixture model (GMM) classifier. A HeartIndex was generated which could objectively differentiate CAD or normal cases. The authors suggest that this technique could be converted into a simple computer software to produce a HeartIndex from images to assist the operator.

Gunasekaran *et al*⁷² conducted a prospective study to examine the relationship of left atrial volume index (LAVI) and major adverse cardiovascular events (MACE) in ACS patients. The baseline LAVI of 75 ACS patients was measured and the patients were divided into two groups of high LAVI and normal LAVI. At 6 months follow-up, the high LAVI group had significantly more MACE than the normal LAVI group with an odds ratio of 1.229.

Cardiac computed tomography angiography

Cardiac computed tomography angiography (CCTA) is an appropriate investigation in symptomatic patients with intermediate or high risk of CAD. It is less invasive than coronary angiography. Ong *et al*⁷³ published a highly cited study on the accuracy of 64-slice multi detector CT (MDCT) evaluating coronary artery disease in relation to coronary calcifications. The study recruited 134 symptomatic patients scheduled for coronary angiography; a 64-slice MDCT evaluation was done on them within 3 months. The patients were grouped into high or low calcium score groups and their MDCT findings were compared with the coronary angiogram results. The authors reported that the low calcium score group had 97.3% correlation and the high calcium score group 90.5% correlation with results of invasive coronary angiography. This study concluded that the degree of coronary calcification correlates with the extent and severity of CAD.

Ibrahim *et al*⁷⁴ recruited patients attending exercise stress test for CAD screening for CT coronary angiography. Dividing the CAD lesions to obstructive (50% stenosis or more) and non-obstructive (less than 50% stenosis), subjects found to have obstructive lesions then underwent conventional coronary angiograms to confirm the findings. The study found that calcium scoring had 100% sensitivity and 97.5% specificity in detecting obstructive CAD at the optimal cut-off value of 106.5 and above. The positive predictive value (PPV) at score 106 and above was 71.4% and the negative predictive value (NPV) was 100%. Calcium scoring was very useful for patients with inconclusive exercise stress test and low to moderate risk.

Chin *et al*⁷⁵ investigated the feasibility of using MDCT to identify the culprit lesion in ACS which would have low overall vessel lumen and plaque density. The authors suggested the concept of "vessel density ratio" (VDR) which is the ratio of mean density of contrast enhancement within a region of interest to mean density of aortic root. 64 subjects of ACS patients of different stratum and stable CAD were recruited for both angiogram and MDCT. They found that culprit lesions in ACS patients had a lower mean VDR compared to non-culprit lesions and compared to lesions in patients without ACS; thus VDR was a good approach to identify ACS culprit lesions.

Sabarudin *et al*⁷⁶ retrospectively analyzed the radiation dose of prospective ECG triggered cardiac CT angiography (CCTA) with different CT generations in 164 patients. The mean effective doses for 128-slice DSCT, 64-slice DSCT, 64-slice SSCT and 320-slice CT scanners were 6.8 \pm 3.2, 4.2 \pm 1.9, 4.1 \pm 0.6 and 3.8 \pm 1.4 mSv respectively. These findings suggest that prospective ECG-triggered CCTA regardless of the scanner generation can achieve low radiation dose, and patient's BMI is the major factor influencing the dose.

Coronary Angiography

Invasive coronary angiography is the gold standard in diagnosing coronary artery disease and is indicated in symptomatic patients at high risk of CAD. Coronary angiography gives information on the anatomy of the coronary arteries and the lesions present in them. However, it does not give information on the viability of the myocardium if it is akinetic i.e. if the myocardium is still alive and would benefit from coronary artery revascularization. Such information is usually obtained by stress echocardiography or cardiovascular magnetic resonance imaging with gadolinium enhancement. Ismail *et al*⁷⁷ investigated the accuracy of using myocardial blush grade (MBG) in assessing myocardial viability during coronary angiography. The authors analysed a total of 135 coronary arteries on coronary angiography done on stable post ACS patients. MBG was scored during angiogram and subsequently dobutamine stress echocardiography was performed with blinding of the angiography results. The authors found 22 coronary arteries with non-viable score (MBG 0). When using dobutamine stress echocardiogram, 17 of the MBG 0 arteries were still viable. The study concluded that using MBG alone in stable post ACS was not sufficient to demonstrate myocardial viability.

One of the known complications of coronary angiogram is contrast-induced nephropathy (CIN) and patients with underlying chronic kidney disease (CKD) are at higher risk. However, it is often detected late as serum creatinine (SCr) rises 2-3 days post contrast administration. Alharazy and colleagues⁷⁸ investigated the accuracy of using serum neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C (CysC) as an early biomarker of CIN. They recruited 100 patients with underlying CKD who were scheduled for coronary angiogram and measured their levels of serum NGAL, CysC and SCr at baseline and at various time points post procedure. The analysis of the ROC curves of the changes in serum NGAL and CysC at 24 hours post procedure from baseline values showed that both can be used for the early diagnosis of CIN.

Fractional flow reserve

Fractional flow reserve (FFR) assessment can be used to grade the severity of coronary lesions during coronary angiography in cases of uncertainty or indeterminate lesions. Yew⁷⁹ highlighted the role of FFR in risk stratification of a complex and high risk case of concomitant triple vessel disease and colon carcinoma requiring early surgery; the team integrated FFR findings to the Syntax score to enable accurate cardiac risk stratification.

Arterial stiffness

Arterial stiffness has been suggested as a marker of atherosclerosis and can be measured in pulse wave velocity (PWV) non-invasively. Alarhabi *et al*⁸⁰ measured the PWV of 92 patients who were undergoing coronary angiogram. He found the mean PWV was higher in patients with CAD than those without CAD. There was also a significant association between the severity of CAD (number of vessels).

TREATMENT OF STABLE CORONARY ARTERY DISEASE

The aim of treatment in stable CAD is to improve symptoms and survival. This primarily involves advice on lifestyle changes and optimal medical therapy with antiplatelet agents, beta-blockers, angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers, and statins. In symptomatic patients, anti-angina medications such as nitrates and calcium antagonists should be started. Patients who continue to be symptomatic or have lesions involving the left main stem or proximal left anterior descending coronary artery should be considered for percutaneous coronary intervention (PCI) or coronary artery bypass grafting surgery (CABG). A survival advantage has been demonstrated with CABG over PCI in patients with left main stem stenosis, or complex 3 or more vessel coronary artery disease particularly in diabetic patients.⁸¹⁻⁸²

Medical treatment

Anti-platelets

Despite the well documented benefit of anti-platelets in CAD, there is a growing concern that the individual's response to anti-platelet therapy varies. Ibrahim *et al*⁸³ investigated the prevalence of anti-platelet resistance in 64 CAD patients and found the proportion of laboratory determined aspirin and clopidogrel resistance was 4.69% and 21.9% respectively. Ibrahim *et al*⁸⁴ measured aspirin resistance in 74 patients with stable CAD on aspirin (52 presented with their first-ever acute event and 22 patients with recurrence). Aspirin resistance was observed in 12 patients (16%) out of the entire cohort, and all but one resistant patient were in the first-ever coronary event group. There were significant correlations between aspirin resistance and age, total cholesterol and LDL levels. The study found no association between aspirin resistance and recurrent coronary events.

The ABCB1 and CYP P450 genes are highly polymorphic and may contribute to the wide inter-individual variability in clopidogrel response. Chua *et al*⁸⁵ reported that in a cohort of 237 patients scheduled for angiogram and possible PCI, the prevalence of ABCB1 3435CT and CYP2C19*2 carriers are high in Chinese ethnicity. However, there was no significant association of the genotypic polymorphisms and platelet activity and one month clinical outcomes.

Tiong *et al*⁸⁶ recruited 237 PCI patients and studied the different pre-PCI clopidogrel regime, genetic prevalence of CYP2C19 polymorphisms, platelet inhibition and 12 month outcomes. They found considerable variations in the loading patterns but regardless of the regime, and even in the presence of CYP2C19 lost-of-function allele carriers, there were no significant difference in platelet inhibition and 12 month outcomes. Further, Mejin *et al*⁸⁷ reported the prevalence and impact of CYP2C19*2, *3 and *17 genotypes on clopidogrel responsiveness among 118 PCI patients who were given dual antiplatelets prior to procedure. There was a diverse inter-ethnic difference in the distribution of CYP2C19 polymorphism which appeared to have a limited impact on clopidogrel responsiveness and clinical outcomes in low-risk patients.

Some studies have shown that proton pump inhibitors and clopidogrel co-prescription increases the incidence of

cardiovascular events and mortality. Tan *et al*⁸⁸ reviewed the available data regarding this controversy and concluded that the available data at the time of writing (2010) was too weak to prove causality.

Beta Blockers

There is good evidence for the use of beta blockers to improve outcomes in CAD patients. Ong *et al*⁸⁹ conducted a retrospective study to assess their centre's usage of beta blockers in post MI patients. A total of 315 patient notes were reviewed; a good percentage of patients (77.5%) were prescribed beta blockers as indicated but doses were optimized only in 39.3% of these patients.

Anti-hypertensives

El Hadi *et al*⁹⁰ investigated the adequacy of hypertension control among 400 ward inpatients and factors affecting hypertension control. Only 24% of patients on admission and 54% on discharge had their blood pressure well controlled (less than 140/90mmHg). Among factors associated with good blood pressure control were use of diuretics, statins and beta blockers. Conversely, the numbers of co-morbidities, cerebrovascular disease, chronic kidney disease, diabetes and Malay ethnicity were associated with poor blood pressure control.

Anti-cholesterol medications

Thuraisingham *et al*⁹¹ randomised 60 patients with hypercholesterolemia treated with simvastatin to either a normal diet or a dietitian guided low cholesterol diet. The authors assessed the effects after 24 weeks and found that a low cholesterol diet did not confer additional advantage on lipid-profile once simvastatin therapy had been instituted.

The REALITY-Asia study⁹² enrolled 2622 new hypercholesterolemic patients in 6 countries including Malaysia and risk stratified them accordingly. The study found that 48% of patients attained their LDL targets and most patients did so within the first 3 months. Increasing age and initial statin potency were associated with success. Al-Khateeb *et al*⁹³ retrospectively reviewed the lipid target attainment of 890 patients and found only 64.2% of patients achieved their respective LDL targets. Similar with REALITY-Asia study, both the studies showed that patients of higher risk were less likely to achieve their LDL targets.

It is known that muscular adverse events occur more frequently with concomitant usage of fibrates and statins. However, switching from one type of fibric acid derivative to another (gemfibrozil to bezafibrate) had not seen any adverse effects prior to the case report of rhabdomyolysis and acute renal failure by Kamaliah *et al*⁹⁴ in two patients with underlying renal impairment.

Dietary supplements

Yusoff⁹⁵ reviewed the available clinical trial evidence in 2002 on the role of Vitamin E supplementation in CAD patients. There were many positive results from various observational studies, dietary studies and animal studies but evidence from good quality, large clinical trials were lacking.

Ong and colleagues⁹⁶ examined the clinical trial evidences of dietary supplement omega-3, red yeast rice and garlic in preventing clinical cardiovascular events. The authors found the GISSI-P and JELIS trials, which were using modest and high dose of omega-3 fatty acids respectively, had convincing evidence. The CCSPS trial studying red yeast rice was reported to have 46% reduction in nonfatal myocardial infarction and coronary death but needed a bigger sample. Garlic products, however, did not reduce cardiac outcomes.

There have been studies on heart failure using a single nutrient or a combination of multiple nutrients but results were inconclusive. Wong and colleagues⁹⁷ recruited 12 heart failure patients with routine medications to study the effect of high dose multiple micronutrient supplementations on their quality of life. The authors followed these cases for a period of 3 to 8 months and administered the Minnesota Living with Heart Failure Questionnaire (MLHFQ). The study found a significant difference between baseline and endpoint of treatments but recommended a further larger, longer term randomized study.

Percutaneous Coronary Intervention

Much advances have been made in the treatment of CAD by percutaneous coronary intervention (PCI). Advances in guide wire, balloon and stent technology has made it technically feasible to treat most coronary stenosis by PCI. It should be noted that the aim of PCI is to improve symptoms; no study has demonstrated a survival benefit with PCI in stable CAD. Ahmad *et al*⁹⁸ reviewed NCVD-PCI data from 2007 to 2009. 10,620 patients underwent 11,498 PCI procedures with 18,116 stents for 15,538 lesions with a 97% procedural success rate. The femoral artery was the commonest percutaneous approach, with the radial artery approach becoming more popular (36% in 2007 to 40% in 2009). 58% of all cardiac lesions had high risk characteristics; post-procedure TIMI grade-3 flow was achieved in 97% of all lesions and the incidence of stent thrombosis was 1%.

Ho and colleagues⁹⁹ examined the patient's anxiety and depression before and after the PCI procedure in their centre using the Hospital Anxiety and Depression Scale. They recruited 61 patients and found that the level of anxiety and depression before and after PCI was low and not significantly correlated with demographic factors.

Ponniah *et al*¹⁰⁰ looked into the predictors of 3 year mortality in 630 PCI patients as captured in NCVD-PCI in 2007. Mortality records were tracked from the National Registration Department from the year 2007 to 2009 and non-cardiac causes of death were excluded. The authors found only renal failure and age group as significant predictors on multivariate analysis. The authors suggested careful evaluation especially for the higher risk older patient and those with renal failure.

Case reports

Yew published a few reports on experiences with various new stent technologies, bioresorbable vascular stents (BVS) and STENTYS platform, and difficult cases of CAD. He described his experience in treating a coronary ectasia case which had atypical coronary anatomy with the STENTYS platform and

BVS.¹⁰¹⁻¹⁰² This new platform had novel self expanding properties, ideal for such lesions but with more challenging technicalities. He also reported his various innovative approaches in deploying a hybrid of overlapping BVS-DES in a long lesion case,¹⁰³⁻¹⁰⁴ application of BVS and STENTYS self apposing stent for complex vein grafts occlusion case,¹⁰² and successful treatment of iatrogenic coronary dissection with paclitaxel coated balloon.¹⁰⁵ In all his reports, he discussed the various issues of choice of stents in the cases, technical deployment and difficulty considerations during the procedures. Sadiq and colleagues¹⁰⁶ reported a rare complication of permanent complete heart block secondary to the loss of first septal perforator after PCI of the LAD and highlight the importance of careful patient monitoring in such cases.

Multi-national studies involving Malaysia

A number of multinational industry sponsored research trials included investigators and patients from Malaysia. Nakamura and colleagues¹⁰⁷ demonstrated the benefit of sirolimus eluting stents (SES) in chronic total coronary occlusion (CTO) over BMS. The study recruited 240 subjects and found SES implantation after recanalisation of CTO resulted in better outcomes. Chan *et al*¹⁰⁸ published the study comparing the SES and BMS in diabetic patients in 2008. The study found the mean 6-month in-stent luminal loss was significantly smaller, and 12-month major adverse cardiac events rate was significantly lower in the SES group.

Kaul *et al*¹⁰⁹ made an outcome comparison between Asians and non-Asians in the everolimus eluting stent (EES) post-marketing surveillance study. The study found that of the 2,700 subjects, the MACE, myocardial infarction and target lesion revascularization rates were lower in the Asian subgroup than in the non-Asian subgroup. The authors noted that this result was driven by good outcomes reported in many centres in India, despite the high prevalence of risk factors.

In 2013, Lee *et al*¹¹⁰ reported on a study on 224 patients with 269 angiographic lesions to study the safety and efficacy of using a long drug-eluting stent (38mm Resolute Zotarolimus-eluting stent) instead of multiple stents. The authors found that the target lesion failure rate using a single-vessel analysis was 4.5% and the rate of stent thrombosis was 0.9%. In patients who are at risk of bleeding, BMS are still widely used to avoid the need for prolonged dual antiplatelet therapy.

Urban *et al*¹¹¹ randomised 2,466 patients who were at increased risk for bleeding to the new polymer-free-drug-coated stent and BMS with only a 1-month course of dual antiplatelets followed by a single agent. The use of a polymer free drug-coated stent achieved better outcomes than BMS.

Coronary artery bypass grafting surgery

Much has advanced in coronary artery bypass grafting surgery (CABG) in recent years. Better surgical techniques, the use of arterial grafts and optimization of medical therapy post CABG has improved graft patency, while advances in anesthetic techniques, better myocardial protection during surgery and improved post-operative care have made CABG

a safe operation with very low morbidity and mortality in most cases. A key difference between CABG and PCI, which explains the better long term outcomes with CABG, is that CABG bypasses entire areas of at-risk myocardium and therefore treats both the local culprit coronary lesion and adjacent at-risk areas, while PCI only treats the targeted local coronary lesion and leaves adjacent areas of at-risk myocardium alone, and is therefore not protective of future progressive CAD.¹¹²

Ishamuddin *et al*¹¹³ conducted a cross sectional study on 137 patients with left main stem disease (LMS), 38% of whom underwent CABG without the use of cardiopulmonary bypass. Less bleeding and blood transfusion were reported in those who underwent CABG without cardiopulmonary bypass with no difference in other outcomes. However, it should be noted that this was a non-randomised study and confounding factors may have influenced the results. There is concern with long term patency of the grafts when CABG is done without cardiopulmonary bypass and this was not accessed in this study.

In another small study, Ooi and colleagues¹¹⁴ compared the outcomes of on-pump (35 patients) and off-pump (29 patients) CABG in patients with pre-existing non-dialysis renal failure. Creatinine clearance worsened in the on-pump group post-operatively but not in the off-pump CABG group. Renal function in both groups were back to baseline at 4 weeks post-operatively.

Park and colleagues¹¹⁵ randomised 880 multivessel CAD patients in 4 Asian countries to either CABG or PCI (everolimus-eluting stents). The authors reported that at 4.6 years, there were significantly fewer myocardial infarctions and repeat-revascularization procedures in the CABG group.

Sokran *et al*¹¹⁶ studied the relationship between hand grip strength (HGS) and myocardial oxygen consumption (MVO₂) index before and after CABG surgery. HGS is a good marker of peripheral muscle function while MVO₂ is an objective measure of functional capacity. The authors recruited 27 patients prospectively prior to their planned CABG and found significant interactions for both HGS (dominant and non-dominant) and MVO₂ before and after CABG. HGS was predictive of functional capacity amongst cardiac patients. There were several limitations with this study particularly the small sample size and short follow-up period.

Case reports

Rare encounters of patients with dextrocardia and "situs inversus totalis" cases were reported. Ismail and colleagues¹¹⁷ reported their case which underwent CABG with total arterial revascularization and Abdullah *et al*¹¹⁸ described their experience with a high risk dextrocardia patient who underwent urgent off-pump CABG. Both reports discussed the different techniques, positioning and approaches needed for dextrocardia during CABG. Raj *et al*¹¹⁹ described a successful CABG in a patient with concomitant diagnosis of asymptomatic Brugada syndrome, highlighting some arrhythmias and precautionary steps taken intra-operatively, and discussing the insertion of ICD for this patient.

Young patients with CAD undergoing CABG were also reported. Ramzisham *et al*¹²⁰ and Lim *et al*¹²¹ both reported CABG on a 29 year old and 20 year old respectively. Ramzisham's patient was a young gentleman with all the CAD risk factors while Lim's patient was a consequence of Kawasaki disease. Both reports discussed the issue of conduit selection in young patients and the need for aggressive control of risk factors for long term graft patency.

A case report on a rare complication of CABG reported by Rahman and colleagues¹²² described a delayed acute Stanford Type A aortic dissection following an off-pump CABG case with pre-existing chronic Type B aortic dissection.

Liew *et al*¹²³ reported their experience with creation of vascular access for dialysis in forearms for two patients who had previously underwent radial artery harvest for CABG. The creation of brachiocephalic fistula (BCF) on one patient and a brachiobasilic fistula (BBF) on the other was successful and no distal hypoperfusion ischemic syndrome (DHIS) was found at 1 year and 6 months follow up respectively.

Stem cell therapy

In recent years, stem cells have been used in an effort to regenerate areas of infarcted myocardium or to stimulate angiogenesis in areas which cannot be revascularised by conventional means. In 2004, Hattori *et al*¹²⁴ reviewed recent advancement in bone marrow cell research and autologous bone marrow mononuclear cells (BM-MNC) transplantation in severe ischaemic heart disease at IJN. The authors claimed bone marrow cell transplantation into myocardium is a safe and effective technique to stimulate development of collateral arteries. Bone marrow mesenchymal stromal cells (BM-MSC) has also been researched locally. However, the limitation is the transportation risk with contamination, infection and reduced viability of the stromal cells. Chin *et al*¹²⁵ published a small study of three cases of intramyocardial MSC injection during open heart CABG using a new technique of culture and transportation. The study reported good cell viability (90% viable) and sterility. Patients were reported to have significant improvement in cardiac function, volume and wall thickness at 6 months. More recently, Musa *et al*¹²⁶ reviewed the current stage of research and development on cell therapies for cardiovascular disease and questioned the efficacy of available evidence on the various types of cells currently used in research settings. The authors recommended avoiding overzealous extrapolation of data reporting and that future studies focus on the biological functions of the available cells lines.

TREATMENT OF ACUTE CORONARY SYNDROMES

Current recommendations for the treatment of ST-elevation myocardial infarction (STEMI) include immediate anti-platelet therapy followed by either primary percutaneous intervention (PCI) or thrombolysis in patients presenting within 12 hours of the onset of symptoms. Primary PCI is recommended over thrombolysis if this can be done within 2 hours of arrival at the hospital as this has been shown to produce higher rates of infarct coronary artery patency, TIMI 3 flow, and lower rates of recurrent ischemia, re-infarction, emergency repeat revascularization procedures, intracranial

hemorrhage, and death. Where primary PCI cannot be performed within 2 hours of presentation, thrombolysis should be performed. A time-dependent reduction in both mortality and morbidity rates has been demonstrated with both reperfusion strategies; it is therefore important for patients to present to hospital as soon as possible after symptom onset, and for hospitals to minimize delays in instituting appropriate treatment on arrival.¹²⁷

Time to presentation

A study was conducted to evaluate if transportation mode affected time to presentation at hospitals. Chew and colleagues¹²⁸ conducted a survey on 110 acute coronary syndrome (ACS) patients and found 95.5% used their own transportation, all of whom did not reach hospital within one hour of the onset of symptoms. Only 3 patients (2.7%) used ambulances and all 3 of them made it within one hour. Level of education and past history of ischemic heart disease did not significantly influence the patient's choice of transportation.

Anti-platelets

ACCORD¹⁹ enrolled 525 patients in Malaysia to evaluate the usage of anti-platelet in unstable angina and NSTEMI patients at discharge and during follow-up visits. During hospitalization and at discharge, aspirin only was used in 86.9%, clopidogrel only in 52.4% and dual anti-platelets in 48.4% of patients. During follow-up visits over one year, the percentage of patients on aspirin only was 62.7–77.6%, on clopidogrel only 5.0–6.8% and on dual antiplatelets 15.6–32.3%.

Huo *et al* conducted the EPICOR Asia,¹²⁹ to follow 13,000 Asian patients admitted with ACS and then discharged home, for up to two years. The study captured the antithrombotic management patterns in Asia, clinical outcomes, healthcare resource use, and self-reported health status. Enrolment was completed in May 2012 and the study findings provided data of the standard and outcome of Asia's management of ACS.

Anti-thrombotics

The rate of bleeding complications secondary to enoxaparin was studied by Mohamed and colleagues.¹³⁰ The study recruited 40 patients who were treated with enoxaparin and prospectively followed up for 3 days in the ward. They found bleeding episodes in 18 patients (45.5%), mainly with hematuria (83.3%). In this small study, the gender of women and renal impairment were associated with higher risk of bleeding.

Reperfusion strategies

Lee *et al*¹³¹ retrospectively reviewed 192 STEMI cases who received thrombolysis using streptokinase and found reperfusion failure rate using ECG criteria of 56.8% associated with diabetes mellitus, hypertension, anterior MI, longer door-to-needle time and high total white cell.

Azlan and colleagues¹³² retrospectively reviewed the incidences and risk factors for bleeding complications post tenecteplase thrombolysis over a 2-year-period. In a total of 100 patients thrombolysed using tenecteplase, 12%

developed bleeding complications. No demographic factors (age, gender and ethnicity) or comorbidities (diabetes, hypertension, hyperlipidemia, previous CVA and previous CAD) were found to be significantly associated with bleeding complications but it must be noted that the sample size of this study was very small. A rare bleeding complication was encountered by Peyman and colleagues¹³³ who described a case report of intraocular hemorrhage post streptokinase administration.

The decision to thrombolyse is usually made by the medical-on-call team. Loch *et al*¹³⁴ assessed the door-to-needle times before and after a change of thrombolysis decision-making, from medical team-led thrombolysis to Emergency Department-led thrombolysis. During the study period of one year for each practice method, 169 patients were thrombolysed by the medical on-call and 128 cases by the ED doctors. Median door-to-needle times were 54 and 48 min respectively. The authors found that the transfer of responsibility for thrombolysis to the ED doctors did not improve door-to-needle times significantly.

Selvarajah *et al*¹³⁵ assessed the impact of variation in cardiac care provision and reperfusion strategies on patient outcomes. They found 75% of all STEMI were treated with thrombolysis, 7.6% underwent primary PCI and the remainder were managed conservatively. Timely reperfusion was low, at 24% in specialized cardiac centers versus 31% in non-cardiologist hospitals and 28% for primary PCI. Cardiac centers had significantly higher use of evidence-based treatments. However, the adjusted 30-day mortality rates for in-hospital thrombolysis and primary PCI were similar at 7%. This was, however, not a randomized study. Similar results were reported by NCVd-ACS 2009-2010¹³⁶ where 74% of STEMI were thrombolysed at presentation and only 7% were directly treated with PCI. Most NSTEMI/UA were treated medically. Only 13% of NSTEMI and 6% of UA were treated with PCI on the same admission. Only 2% of NSTEMI and 1% of UA underwent CABG on the same admission.

Adherence to clinical guidelines

Kassab and colleagues¹³⁷ retrospectively reviewed the practice adherence to clinical guidelines in 380 ACS patients focusing on the medical treatment: aspirin ± clopidogrel, beta-blockers, statins and angiotensin-converting enzyme inhibitors (ACEI) / angiotensin II receptor blockers (ARBs). They found 95.7% of the patients received antiplatelets comprising of at least aspirin, 82% received aspirin plus clopidogrel, 80.3% of the patients received a beta-blocker at discharge, 95% received a statin and 69.7% received either an ACEI or ARB. The authors concluded that there was good adherence to guidelines for the secondary prevention of CAD after an ACS.

Hassan *et al*¹³⁸ conducted a study on the role of pharmacists in the secondary prevention therapy in ACS patient management. Using a pre-intervention adherence audit as baseline, they investigated the effect of placing two hospital pharmacists in the ward rounds with physicians. A total of 72 interventions were made by pharmacists of which drug initiation was the most common (59.7%), followed by recommendations to switch drugs (23.6%) and dose

optimisation (16.6%). Most recommendations (72.2%) were accepted by clinicians. The intervention also led to a significant increase in the utilization rates of all four drug classes (from 42.6% to 62.6%) underlying the important role of ward pharmacists in improving clinical care.

Patient adherence

There were a number of studies looking into patient adherence with medications and health recommendations. Leong *et al*¹³⁹ assessed the level of adherence using a semi-structured questionnaire in 52 post MI patients and found all the responders did adhere to medications as prescribed. However, only 80% adhered to healthy diet advice; there was low adherence to weight loss (25%), physical activity (65.4%), social activity (44.2%), smoking cessation (28.8%) and alcohol use (19.2%) advices.

Lee and colleagues¹⁴⁰ surveyed 210 ACS patients using the Medical Outcome Study Specific Adherence Scale (MOSSAS) questionnaire on patients' recalled health recommendations. The study found suboptimal adherence rate of 65.2% and it varied from 22.1% to 95.1%. Kassab *et al*¹⁴¹ prospectively followed up 190 ACS patients' level of adherence to evidence-based therapies at 6 months after discharge using the translated eight-item Morisky Medication Adherence Scale (MMAS). The study found 18.4% reported high adherence, 51.1% medium adherence and 30.5% low adherence. Older, unemployed, multiple comorbidities and polypharmacy are associated with poorer adherence. The same group¹⁴² continued the follow-up for another 2 years and managed to retain 151 patients from the original cohort. There was a significant downward trend in the level of adherence to medications during the 2 years period from a mean MMAS score of 6.39 at 6 months to 5.72 at two years. The authors concluded that long-term adherence to secondary prevention therapies among patients with ACS in Malaysia was suboptimal.

Poor patient adherence is detrimental to the long term outcome and studies looked into ways to improve this. Khonsari *et al*¹⁴³ studied the effect of automated SMS-based reminders on medication adherence in ACS patients after hospital discharge. They randomized 62 patients with ACS into two groups, with one group of patients receiving SMS reminders and the other with usual care as control, for a period of eight weeks after discharge. The study found that the intervention group had higher medication adherence level than the usual care group.

Outcomes

The NCVd-ACS 2009-2010 reported that in-hospital mortality rates of ACS patients remained consistent between 6-8% over the five-year period from 2006 to 2010, with overall average of 7%. Mortality of STEMI was 9% while NSTEMI was 8%. These were higher compared to several other global and regional ACS registries.

Patients who presented with suspected diagnosis of ACS are triaged to red zone for faster treatment. Ahmad and colleagues¹⁴⁴ examined the diagnosis and one week mortality rate of all red zone patients at Hospital University Sains Malaysia and found that out of a total of 440 red tag

patients, 54% of them were cardiac related cases. At one week follow-up of these cases, 6.1% died within a week and 44% of their deaths were due to ACS.

Ho *et al*¹⁴⁵ studied the quality of life of 108 ACS patients using the Medical Outcomes Short Form 36 (SF-36). The study found that respondents had a good quality of life (mean total score 59±22); the general health components was associated with education level while physical components were associated with income level.

Selvarajah and colleagues¹⁴⁶ examined the Thrombolysis In Myocardial Infarction (TIMI) risk score for STEMI. Using the NCD-ACS 2006-2008 data, the authors found TIMI risk score was strongly associated with 30-day mortality with good discrimination for the overall study population and also the high risk subgroups. Calibration was good for the overall study population and diabetics, but poor for those with renal impairment; it may be due to the small size of the subgroup. The authors concluded that TIMI risk score is valid to be used in our population.

COMPLICATIONS OF CORONARY ARTERY DISEASE

Heart failure

Chong *et al*¹⁴⁷ conducted a prevalence study of heart failure (HF) among all medical admissions and found HF accounting for 6.7% of all medical admissions with an inpatient mortality rate of 11%. CAD was the main etiology (49.5%) followed by hypertension (18.6%). The authors found ACE inhibitors were under-utilized in our HF population.

Sudden death

Sudden death in chronic heart failure patients is common and can be prevented with implantable cardioverter-defibrillators (ICD). Prophylactic ICD is costly and invasive, often instituted based on several predictors of sudden death such as a very low left ventricular ejection fraction (LVEF). Yap and colleagues¹⁴⁸ pooled available data of 2,828 patients to examine the dichotomy limit of LVEF for ICD treatment. The authors suggest that no single dichotomy limit is satisfactory and patients with too low a LVEF (less than or equal to 10%) would not benefit from ICD treatment; cost effectiveness was maximal in those with LVEF between 16 and 20%.

Psychological

Ho *et al*¹⁴⁹ administered Hospital Anxiety and Depression Scale (HADS) questionnaires to 108 ACS patients to determine the prevalence of anxiety and depression. The study found low scores for both anxiety and depression, and significant difference in scores when participants stratified for marital status and comorbidities. Satpal *et al*¹⁵⁰ recruited 189 CAD patients to establish the factor structure of HADS. The authors found that HADS was good and valid in terms of factor structure and internal consistency to measure the psychological distress among CAD patients and recommended that the cut-off score to screen for psychological distress be re-evaluated.

Sharmini *et al*¹⁵⁰ examined the relationship between social support, depressive symptoms and quality of life among

women with CAD. They interviewed 50 CAD patients in the outpatient clinic using a questionnaire comprised of various scales and interviewed another 10 CAD patients with open-ended questionnaire for qualitative analysis. The study showed that informational support is significantly predictive of depressive symptoms. Qualitative analysis showed that social support improved quality of life and enhanced emotional well being. These factors should be considered in designing cardiac rehabilitation programmes.

Patient's subjective experience and changes in life following myocardial infarction were examined by Sukeri *et al*¹⁵¹ using qualitative research. The study interviewed 11 Muslim respondents to investigate the impact of MI from the perspective of Muslim respondents. The respondents commonly reported post-MI stresses such as fear and anxiety. The influence of religion was evident and appeared to be intertwined in many aspects of their feelings on lives and illness.

HEALTH COST

Aniza and colleagues¹⁵² compared the cost to treat patients with uncomplicated AMI using two different methods, namely step down costing and activity based costing (ABC) in 2011. They found the cost of treatment (with PCI) using step down costing was RM17,290 and using ABC method RM20,431.39. Cost of treatment calculated by using ABC is higher by 15.3% than the step down costing.

SECTION 2 - RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Considerable research on CAD has been done in Malaysia. The evidence continues to show that CAD is the major cause of mortality and morbidity in the country. A high prevalence of risk factors for CAD is present in the population. Greater efforts must be made towards education of the public to change dietary habits and other at risk lifestyles such as smoking, and to increase awareness of healthy living such as regular exercise, etc, to reduce the prevalence of CAD in the country. Greater efforts at secondary prevention are also needed to improve outcomes once CAD is diagnosed. However, studies have shown that the adherence of patients in this country to primary and secondary prevention strategies and treatments was not high.¹³⁹⁻¹⁴³ Steps must be taken to find ways to improve patient adherence, which may necessitate spending a longer time with patients during clinic consultation, setting up specialist CAD clinics for this purpose, and financial incentives or disincentives.

Two studies¹³⁵⁻¹³⁶ in this review showed that patients presenting with STEMI in this country are typically treated by thrombolysis, contrary to current guidelines which recommend primary PCI as the preferred treatment due to its better outcomes.¹²⁷ Much efforts are needed to improve cardiology services in the country with provision of primary PCI facilities in all major cities. Earlier instituting of appropriate treatment has been shown to lead to better outcomes. One study identified mode of transportation as a factor in delayed presentation to hospital following onset of symptoms.¹²⁸ Better education of the public on the symptoms

Table I: Summary of risk factor prevalence studies in Malaysia

Authors	Study type	Population studied (Location)	Year (of study unless specified)	N	Risk factors findings
Ahmad <i>et al</i> ¹⁹	Prospective	Unstable and NSTEMI patients (17 participating Hospitals)	2004-2005	525	Hypertension (66.1%), Diabetes Mellitus (38.9%), Dyslipidemia (40.4%), Smoking history (Current smoker: 21.7%, ex smoker: 25.3%), previous history of CAD (64.4%), family history of CAD (15%)
Chiam <i>et al</i> ¹⁴	Retrospective	Post CABG patients (HUKM)	1998-2001	302	Hypertension (78.8%), Diabetes Mellitus (45.7%), Hyperlipidemia (89.1%)
Suleiman <i>et al</i> ¹⁸	Case Control	Adult male patients admitted to medical ward (HKL)	1994-1995	102	Smoking >20 sticks/day (OR 9.49 (CI 95% 2.91,40.81), Hypercholesterolemia (OR 21.26 (CI 95% 8.01,125.53).
Nawawi <i>et al</i> ²⁰	Cross sectional	Adult Malays in rural population in Raub, Pahang (30 to 65 years old)	1997-1999	609	Hypertension (30.3%), Diabetes Mellitus (6.4%) Impaired fasting glucose (13.9%), Dyslipidemia (67.3%), Smoking (24.4%), Overweight/obesity (44.7%), Increased waist hip ratio (48.5%)
Mohd Yunus <i>et al</i> ²¹	Cross sectional	Adult Malays in rural population in Dengkil, Selangor (15 years old above)	1999	570	Hypertension (28.6%), Smoking (21.1%)
Chang <i>et al</i> ²²	Cross sectional	Adults in rural Sarawak (20 to 65 years old)	published in 2012	260	Hypertension (13.5%), Diabetes Mellitus (1.5%), Smoking (15.4%), Hypercholesterolemia (22.6%), Overweight (39.6%), Obesity (11.9%)
Norazmi <i>et al</i> ¹¹	Cross sectional	Fisherman community in Kelantan	1994	223	Hypertension (28.8%), Smoking (76.5%), Low HDL (95.8%)
Lua <i>et al</i> ¹²	Cross sectional	Security guards in UM	2003	130	Hypertension (21.7%), Diabetes Mellitus (11.3%), Hypercholesterolemia (74.8%), Smoking (40.5%), Overweight (47.8%), Obesity (14.8%)
Nazri <i>et al</i> ¹³	Cross sectional	Adult factory employees in Kota Bahru, Kelantan	2003-2004	148	Hypertension (shift workers group: 22.4%, day workers group: 4.2%).

and signs of acute coronary syndromes and the urgency and best way to get to hospital is needed, as well as improving our emergency ambulance service.

SECTION 3 - FUTURE RESEARCH DIRECTION

There is an absence of research on both primary and secondary prevention strategies and treatments in the country. Such studies are needed to determine their feasibility and effectiveness in reducing CAD in the country, and improving its outcome once diagnosed. Studies are also needed to better understand why patient adherence to primary and secondary prevention strategies and treatments are not as good as it can be in this country, and how this can be improved.

There is an absence of data on the long term outcomes following both PCI and CABG in the country. Although such data is available from elsewhere, particularly the western developed countries, it is important that the long term outcomes in this country are also known to ensure that our patients are benefiting from these invasive treatments. To this end, the newly launched National Thoracic and Cardiovascular Surgical Database (NCTSD) Registry should hopefully be able to provide long term outcomes of CABG in a few years time. There is also a need for the NCVS-PCI registry to collect and report on long term outcomes following PCI.

There have been very few studies in the country on the mode of coronary artery revascularization in patients who need this. Current evidence demonstrate a survival benefit with CABG over PCI in patients with 3 or more vessel coronary artery disease and complex coronary artery anatomy particularly if the patient is diabetic.⁸¹⁻⁸² Studies are needed to evaluate the current practice in the country, and whether current guidelines are being adhered to.

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A Review of Stroke Research in Malaysia from 2000 – 2014

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ABSTRACT

Over 100 articles related to stroke were found in a search through a database dedicated to indexing all literature with original data involving the Malaysian population between years 2000 and 2014. Stroke is emerging as a major public health problem. The development of the National Stroke Registry in the year 2009 aims to coordinate and improve stroke care, as well as to generate more data on various aspects of stroke in the country. Studies on predictors of survival after strokes have shown potential to improve the overall management of stroke, both during acute event and long term care. Stroke units were shown to be effective locally in stroke outcomes and prevention of stroke-related complications. The limited data looking at direct cost of stroke management suggests that the health economic burden in stroke management may be even higher. Innovative rehabilitation programmes including brain-computer interface technology were studied with encouraging results. Studies in traditional complementary medicine for strokes such as acupuncture, *Urut Melayu* and herbal medicine were still limited.

KEY WORDS:

Stroke, Malaysia, risk factors, presentation, diagnosis, stroke unit, treatment, cost, rehabilitation, survival, outcomes

INTRODUCTION

Stroke is a significant global health problem, contributing to major morbidity and mortality for both developed and developing countries. Worldwide, stroke was ranked as the second commonest cause of death and the third most common cause of disability-adjusted life-years (DALYs) from the Global Burden of Diseases, Injuries and Risk Factors Study (GBD) in 2010.^{1,2}

Over 100 articles related to stroke were found in a search through a database dedicated to indexing all literature with original data involving the Malaysian population between years 2000 and 2014 using the medical subheadings (MeSH) Stroke, and Ischemic Attack, Transient.³

SECTION 1: STROKE EPIDEMIOLOGY IN THE COUNTRY

Before the year 2000, when compared with eight other Asian countries, Malaysia was ranked as a country with incomplete epidemiological data for stroke, consisting mainly of hospital-based information.⁴ Over the following decade,

reports on stroke epidemiology in the country were derived from vital registry, hospital-based information, and observational studies from local hospitals. It was not until 2009 when the National Stroke Registry was established. This initiative aims to collect basic epidemiological data, as well as to guide the planning and implementation of stroke prevention and intervention programmes.

In Malaysia, stroke was the second leading cause of death according to the Malaysian National Burden of Diseases Study and study on vital registry system in 2000.^{5,6} In comparison, using empirical data from vital registry systems in 2000, stroke was reported as the leading cause of death in Indonesia, Myanmar, Vietnam and Thailand.⁶ Loo and Gan, however listed stroke as the third leading cause of mortality for males in Malaysia, in 2009, after ischaemic heart disease and pneumonia, while it ranked second for females after ischaemic heart disease.⁷

During the third National Health and Morbidity Survey (NHMS) in 2006, the prevalence of stroke was estimated to be 0.3% among Malaysians.⁸ In the fourth NHMS survey in 2011, the prevalence of stroke was reported as 0.7%, with 1.7% among those aged 55-59 years, 2% in 60-64 years, 3% in 65-69 years, 3.5% in 70-74 years and 7.8% in 75 years and beyond.⁹ The same survey also illustrated higher prevalence of stroke among those divorced or widowed (2.5%) compared to single (0.1%) and married (0.9%) but no significant difference across gender and ethnicity.⁹ The first stroke incidence study in Malaysia was conducted in the South West District of Penang Island between April 2010 and March 2011.¹⁰ The overall age-standardized stroke incidence in the study region was 67 per 100,000 persons. More than half (53.1%) were males and nearly a quarter (23.7%) were recurrent strokes.

A survey on all Malaysian pilgrims going to Mecca in 2003 revealed that 3.9% of elderly pilgrims aged ≥ 65 years had a previous stroke.¹¹ In a study involving 40 elderly aged ≥ 60 years from nursing care centres in Klang Valley, 75% of males and 64.4% of females self-reported that they had history of stroke.¹²

Age and gender

Differences have been noted in the demographic characteristics, stroke subtypes and pathological distribution of vascular lesions between Asian and Caucasian populations. Stroke patients in Malaysia were generally

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Table I: Demographic characteristics of stroke patients reported in various centres in Malaysia

Study	Location	Study period	Study subjects	Mean age (years)	Male gender	Ethnicity			
						Malay	Chinese	Indian	Others
Jaya F <i>et al</i> ¹³	Kelantan	Jan 97' – Dec 98'	158*	59.3	58.2%	86.1%	13.9%	-	-
Ong TZ and Azman Ali R ¹⁴	Penang	Dec 98' – Nov 99'	246	65	56.5%	28.9%	55.7%	14.2%	-
Basri H and Azman Ali R ¹⁵	Kuala Lumpur	Jun 00' – Jan 01'	218	62.2	48.2%	37.2%	74.8%	8.3%	2%
Tan KS <i>et al</i> ¹⁸	Kuala Lumpur	Jan 07' – Mac 08'	67**	41.5	58.2%	46.5%	21.1%	32.4%	-
Grover CS and Thiagarajah S ¹⁶	Miri	Jun 08' – May 09'	215	62.5	60.5%	16.3%	28.4%	-	Iban 37.2% Others 18.1%
Nazifah SN <i>et al</i> ¹⁷	Penang and Terengganu	Aug 09' – Dec 10'	1018	62.5	54.3%	83.7%	11.1%	4.2%	1%
Neelamegam <i>et al</i> ¹⁰	Penang	Apr 10' – Mac 11'	228	Age stratified	53%	-	-	-	-
Loo KW and Gan SH ⁷	Kelantan	Apr – Aug 11'	57	54.5	-	100%	-	-	-
Tan KS <i>et al</i> ¹⁹	Kuala Lumpur	Dec 11' – May 12'	35**	41.1	60%	-	-	-	-

*Study only involved patient with first ever stroke.

**Study involved only young patients with ischaemic stroke aged between 18 and 49 years.

Table II: Complication prevalence rates according to ward of admission in ten Asian countries, including Malaysia (Total N= 1153) (selected 10 most common complications)

Complications	Stroke Unit (%)	General neurology ward (%)	General medical ward (%)
Recurrent stroke	1.5	2.6	29.0
Depression	1.1	2.2	23.0
Constipation	4.6	0.1	17.0
Urinary retention	3.0	6.0	16.0
Falls	0.2	2.6	9.2
Urinary tract infection	1.8	8.8	7.4
Chest infection	1.5	16.9	7.4
Aspiration	1.8	2.4	4.0
Pressure sore	0.9	3.8	3.1
Deep vein thrombosis	0.2	0.2	1.5

younger. The mean age of stroke onset in Malaysia was between 54.5 and 62.6 years^{7,13-17} (Table I). Males accounted for 48.2% to 60.5%.^{7,10,13-17} The different proportions in ethnicity across all the studies reflected the geographical variation in ethnic distribution, rather than ethnic-specific prevalence in the country.

A comparison of the Malaysian and Australian stroke registries on young adults aged between 18 and 49 years, showed comparable age of onset as well as gender ratio for ischaemic stroke.¹⁸ The mean age was 41.5±8.8 years for Malaysia and 40.1±8.8 years for Australia with a sex ratio of male to female 1.4: 1 and 1.54: 1, respectively.

Stroke classifications

Up to two-third of reported stroke cases in Malaysia were of ischaemic origin, with the remaining one-third being haemorrhagic (intracerebral and subarachnoid haemorrhages).^{10,13-17} In a single centre prospective study, among all stroke patients admitted to Penang Hospital over one-year period, 74.8% were ischaemic and 25.2% haemorrhagic in origin.¹⁴ This result was reproduced in two other larger studies across the country where ischemic stroke

was reported in the range of 73.3% to 79.9%.^{10,17} Malaysia had a higher proportion of haemorrhagic strokes compared to higher income countries.^{10,15} More patients who defaulted antihypertensive treatment had haemorrhagic stroke compared to ischaemic stroke.¹⁶

Based on the Oxfordshire Community Stroke Project (OCSP) classification, between 2009 and 2010, the Malaysian National Stroke Registry involving two tertiary hospitals in Terengganu and Penang reported that 43.4% of ischaemic stroke patients had partial anterior circulation infarct (PACI), 27.4% had lacunar infarct (LACI), 16% had total anterior circulation infarct (TACI), 7% had posterior circulation infarct (POCI) while 6.2% were unclassified or uncertain.¹⁷ These findings were slightly different from earlier studies. In the late 1990's, 33% of patients with cerebral infarcts in Kelantan were LACI, followed by TACI (28%), PACI (24%) and POCI (15%).¹³ In 2000, a study in Kuala Lumpur reported nearly half of their ischaemic stroke patients suffered from lacunar infarct (46.8%), followed by middle cerebral artery (MCA) infarct (14.2%).¹⁵ Up to 38% had cerebral infarcts over right hemisphere, 35.7% left hemisphere, 17.6% both hemispheres and 6.3% cerebellar region.¹⁷

SECTION 2- STROKE-RELATED RISK FACTORS

Hypertension was the commonest risk factor for stroke (53.2–76.1%) followed by diabetes mellitus (27.4–55.2%) and hyperlipidaemia (4.8–37.3%) across various local studies.^{14,16-18,20-22} Other reported risk factors for stroke in Malaysia were smoking (19.4–37.3%), ischaemic heart disease (10.4–35.5%), a history of previous stroke or transient ischaemic attack (TIA) (7.5–25.1%) and chronic kidney disease (10.4%).^{13,17,18,21,23}

A one-year review of medical records in Besut, a district hospital in the state of Terengganu, showed that 92% of stroke patients aged ≥ 50 years, and males (52%) were affected more than females.²¹ The prevalence of all risk factors such as hypertension, diabetes, dyslipidemia and heart diseases was higher among males.²¹ Nonetheless, as high as 20.9% patients with stroke had no identifiable risk factors.¹³

A review article looking into hypertension and stroke prevalence, control and strategies in Asia found that hypertension and stroke tend to occur at younger age in Asians compared to Westerners, and that the risk of hypertension increases at lower body mass index (BMI) of 23–25kg/m².²⁴ It also concluded that being overweight, sedentary behaviour, alcohol, higher social class, higher salt intake, diabetes and smoking are common risks factors for hypertension and stroke in most Asian countries.

The presence of atherosclerotic disease may also predict increased risk of stroke. Peripheral artery disease (PAD), a manifestation of atherosclerosis was found to be highly prevalent (23%) among high risk patients (established cardiovascular disease, ischaemic stroke or diabetes mellitus for at least 5 years) in Malaysia.²⁵ But, only 27% of them were symptomatic with classical intermittent claudication. PAD was found in patients with pre-existing cardiovascular disease (33%), ischemic stroke (28%) and diabetes (27%).²⁵

Guo Y *et al.*, in their review involving studies conducted in the Far East (Japan, Taiwan, China and South Korea) and Southeast Asia (Singapore), reported that the rate of stroke related to atrial fibrillation (AF) was 13.0–15.4% in the community.²⁶ The rate varied between 3.1% and 24.2% in studies involving hospitalized patients. This was in accordance with local studies where 6.1–10.6% of stroke patients admitted to tertiary centres had AF.^{19,22,23}

Hyperhomocysteinemia is a potentially modifiable risk factor associated with a significant proportion of atherothrombotic ischaemic strokes in the Malaysian population. It is postulated that a high level of homocysteine induces direct endothelial injury causing endothelial dysfunction and accelerates atherogenesis and thrombogenesis, contributing to ischaemic stroke. In a pilot project involving 83 stroke patients, the mean plasma homocysteine level was 13.5 μ mol/l.²⁷ About 30% had moderate hyperhomocysteinemia ($>15.2\mu$ mol/l). Moderate hyperhomocysteinemia was shown to be an independent risk factor for stroke with an odds ratio (OR) of 5.3. Besides, there was a graded association where the stroke risk increased with the higher level of homocysteine.²⁷ This finding was

reinforced in a larger case-control study involving 292 subjects.²⁸ The homocysteine level was significantly higher in the stroke group (11.35 \pm 2.75 μ mol/L) compared to the control group (10.38 \pm 2.79 μ mol/L) ($p=0.001$). The authors also showed that TT genotype of the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphic gene was an important determinant for homocysteine levels in Malaysian ischemic stroke patients.²⁸ However, no significant difference was noted in the rate of hyperhomocysteinemia, as well as prevalence of C677T polymorphism among stroke patients between the different ethnic groups.

Arteriovenous malformation (AVM) in the brain may pose a risk to hemorrhagic stroke. A cross-sectional study revealed that brain AVM occurred predominantly in young males (65.5%), and 69% presented with intracranial haemorrhage.²⁹ There was an association between the AVM architecture and risk of intracranial bleed. Significant factors include small nidus size ≤ 3 cm, deep location of AVM and deep venous drainage.

Subclinical cerebral infarcts (SCI) have been increasingly shown to cause significant impact on clinical outcome. SCI are lesions which share neuropathologic and neuroimaging characteristics with cerebral infarcts but without any recognized clinical symptoms of acute stroke. SCI are associated with risk of future stroke, stroke recurrence, cognitive impairment and functional disability. One-third of ischaemic stroke patients attending an outpatient clinic at a university hospital in Kuala Lumpur had SCI.³⁰ Hypertension, diabetes and leukoaraiosis were shown to be independent risk predictors of SCI. These factors were postulated to be responsible for the progression of atherosclerotic and lyphohyalinotic changes in small arteries in the brain causing dysregulation of cerebral flow and metabolism, leading to small silent cerebral infarcts.³⁰

In a comparative study looking at stroke aetiology based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification between 67 Malaysian and 61 Australian young ischaemic stroke patients. Tan KS *et al.* reported that Malaysian patients tend to have large vessel atherosclerosis (28.3%) and small vessel occlusion (32.8%), while the Australian counterparts had a greater proportions of cardioembolism (21.3%) and vascular dissection (11.5%).¹⁸ Cardioembolic cause accounted for 12.9% of ischaemic strokes in the Malaysian series, while 4.2% could be attributed to cerebral venous thrombosis.¹⁸ On the other hand, the National Stroke Registry reported more than half of cerebral infarcts were of large vessel diseases (58.9%), followed by small vessel disease (28.3%), undetermined causes (10.1%) and cardioembolism (3.4%).¹⁷

As for the rare causes of strokes, local authors have reported cases which included atrial myxoma where a young gentleman presented with sudden onset of weakness with cerebellar signs,³¹ coarctation of aorta,³² silent meningioma after cardiopulmonary bypass surgery,³³ angioinvasive cerebral aspergillosis in a patient with diabetes,³⁴ and paradoxical embolism across solitary pulmonary arteriovenous malformation with feeder vessels.³⁵ A case of

migrainous infarction involving bilateral occipital lobe and migraine-triggered seizure likely precipitated by oral contraceptive pills in a patient with migraine and visual aura has been reported.³⁶ Apart from migraine, drug abuse such as methamphetamine,^{19,37} and systemic lupus erythematosus¹⁹ were rarely identified as risk factors in young ischaemic stroke.

SECTION 3- MANAGEMENT FOR ACUTE STROKE AND POST-STROKE SEQUELAE

Clinical manifestations

Stroke is a clinical diagnosis. The majority of patients presented with unilateral body weakness (90.5%), followed by weakness and seizures (21.4%).³⁸ Other clinical presentations such as headache, vomiting, visual loss and slurring of speech have also been reported.³⁸

Clinically it may be difficult to differentiate hemorrhagic from ischemic brain infarcts. Validation work by Kan CH *et al.* showed that Siriraj Stroke Score was not a reliable tool for differentiating intracerebral haemorrhage from infarction following an acute stroke at presentation.³⁹

While the majority of stroke patients will present with features of focal neurological deficits, occasionally stroke could present with hyperkinetic disorders. Tai ML *et al.* described a case of a 78-year old man who developed sudden onset of right hemiparesis followed by abnormal involuntary movements involving right upper and lower limbs.⁴⁰ His hemiballistic movements were present at rest and worsened with action. Kiu KY *et al.* reported a 57-year old man with bilateral recurrent occipital infarcts presented with cortical blindness and Anton Syndrome (visual anosognosia), where he denied loss of vision although he was unable to see.⁴¹

Many diseases may have clinical features that could be confused with stroke. They are known as stroke mimics. A case discussion on possible tuberculous meningitis with stroke-like presentation was described by Gnanasan S *et al.*⁴²

Stroke may mimic other non-vascular conditions. Hasan S *et al.* described a young lady without any vascular risk factors who presented with features of Miller Fisher syndrome which was later diagnosed to be an acute right medial thalamic infarct.⁴³ The lady recovered completely in one month with standard stroke treatment.

Sapiah S and Hamidon BB reported a case of an Englishman in Kuala Lumpur, who had suffered from possible Creutzfeldt-Jakob disease diagnosed by electroencephalograph.⁴⁴ He had history of recurrent stroke, hypertension and hypercholesterolaemia. He presented with progressive deterioration in cognitive function, a symptom that could be attributed to repeated vascular insult from previous strokes, as well as gait disturbance and cerebellar signs. Therefore, it is important for physician to realize that other neurological conditions may affect stroke patients and vice versa. A thorough history and physical examination are essential in patient's assessment.

Investigations and diagnostic modalities

Brain computed tomography (CT) scan remains as the imaging modality for stroke in most centres in Malaysia. Radhiana H *et al.* described the Alberta Stroke Program Early CT Score (ASPECTS) as a systematic, robust and practical method that could be adopted for detection and reporting of the extent of acute ischemic stroke, in order to overcome challenges in infarct volume estimation in patients eligible for thrombolysis.⁴⁵ This scoring system correlates inversely with stroke severity and functional outcomes, but limited to assessment of MCA territory infarct. CT perfusion (CTP), a newer investigative method, was shown to be a useful imaging tool for determining acute cerebral infarction by Man K *et al.* who found that the prevalence of normal unenhanced CT but positive CTP for cerebral ischemia was 22.7%.³⁸ The same study also reported the mean time of patients presented for scan was 10.5±7.4 hours, with 11.9% of them presented within 4 hours of symptoms onset, 26.2% between 4 and 5.9 hours, and the remaining 73.8% after 6 hours.³⁸ A systematic review on cerebral CT angiography (CTA) and CTP in detecting acute stroke, by Sabarudin A *et al.*, revealed that CTA offers high diagnostic accuracy in detecting the site of occlusion and assessing its severity, whereas CTP provides high specificity in detecting ischaemia, and differentiating infarcts and ischaemic penumbra, which can facilitate decision making in thrombolytic therapy.⁴⁶

In the last decade, the utilization of transcranial doppler (TCD) technologies in the field of stroke has gained interest of neurologists worldwide. Tan KS *et al.* reviewed the potential use of TCD in the diagnosis and prognostication of ischaemic stroke and TIA, and may be routinely applied for asymptomatic patients at high risk of stroke.⁴⁷ This non-invasive, reproducible, sensitive and specific technology allows detection of arterial occlusion and recanalization offers real-time monitoring capability.

Several haemostatic biomarkers have been investigated for acute stroke at presentation. Tissue plasminogen activator (tPA) antigen, a fibrinolytic marker was found to be higher in acute stroke patients (OR=4.6) compared to the controls.⁴⁸ The higher level of tPA probably indicated a poor prognosis, as all patients who died within one month of stroke onset had high tPA. Besides, micro-RNAs have emerged as potential biomarkers in diagnosing and prognosticating ischaemic stroke. Interestingly, these stably expressed, dysregulated molecules continued to be detectable up to 18 months after stroke onset.⁴⁹ Circulatory microRNA-145 expression which is recognized as a marker and modulator of vascular smooth muscle cell phenotype has been shown to be significantly higher in patients admitted with acute ischemic stroke.⁵⁰ It was hypothesized that upregulation of microRNA-145 might be an indicator of good outcome in vascular regeneration to achieve homeostatic equilibrium. However, the role of this biomarker in clinical practice is yet to be elucidated.

Prevention and treatment strategies

Prevention

Rabia K *et al.* briefly discussed the importance of primary prevention for stroke. They emphasized risk factors management such as lifestyle modifications, measures to control hypertension, dyslipidemia, diabetes and AF.⁵¹ For

secondary stroke prevention, they discussed the importance of blood pressure control, treating dyslipidemia and diabetes to target, as well as roles of antiplatelets therapy and carotid endarterectomy.⁵¹ The newly proposed pooled cohort risk scoring to estimate 10-year atherosclerotic cardiovascular disease risk, including fatal and non-fatal stroke, was retrospectively validated in a tertiary primary care setting.⁵² It was incorporated as part of the new blood cholesterol management guideline from the American College of Cardiology and American Heart Association.

Roles of stroke unit and stroke education

Improved assessment procedures and early rehabilitation could be the explanation for better outcome observed if stroke patients are admitted to stroke unit compared to general medical or general neurology wards. Complication prevalence rates comparing stroke unit, general medical ward and general neurology wards are illustrated in Table II.⁵³ Acute stroke units have been set up in some tertiary hospitals in Malaysia to date.⁵⁴

There is an increasing effort to promote community awareness to detect stroke symptoms and to enhance responsiveness to a stroke patient's need. A local acronym, of equivalent to FAST (facial drooping, arm weakness, speech difficulties and time), has been developed by the Kuala Lumpur Regionalized Integrated Stroke Intervention System (KRISIS) team for this purpose. The acronym is "MATA", in Malay, stands for "Muka" (Face), "Angkat Tangan" (Lifting arm), "Tutur" (Speech), "Angkat Telefon" (Dialing telephone).⁵⁵ The effectiveness of such promotion at community settings is to be evaluated.

Hassan NH *et al.* conducted a cross sectional study among stroke patients, caregivers and therapists to design a website to deliver stroke information using user-defined two-level hierarchy web navigational structure based on Malaysian perspectives.⁵⁶ This approach paves the way for designing an informative, interactive and user-centred website to enhance stroke education in our community.

Cost analysis for stroke care

Stroke carries a substantial socio-economic burden to individuals, family and society. Aznida FAA *et al.* studied the cost of treating an acute ischemic stroke from admission to the out-patient follow-up at a teaching hospital.⁵⁷ The average in-hospital length of stay was 9.8 days for major strokes and 3.6 days for minor strokes. There was an average of two outpatient clinic visits per patient in three months period. Outpatient rehabilitation involved 10 and 15 sessions for minor and major stroke respectively over six months. The calculated costs for hospital admission were MYR 9000 and MYR 3353 for a major and minor stroke, respectively. In outpatient setting, the costs were calculated to be MYR 103 for each specialist clinic visit and MYR 43 for one rehabilitation therapy session per patient, regardless of stroke severity.⁵⁷

In another cost analysis study, Nor Azlin *et al.* reported the mean cost of care per patient in a teaching hospital being MYR 3696.40 or 16% of per capita gross domestic product (GDP) of the country.⁵⁸ The cost was attributable mainly to human resource amounting to MYR 1343.90 (36.4% of total

direct medical cost), followed by medications (MYR 867.30 or 23.5%) and laboratory services (MYR 337.90 or 9.2%).⁵⁸ The most severe stroke consumed higher cost than mild stroke, by MYR 1598.10

Ramesh S *et al.* in his reply letter to Nor Azlin *et al.* stressed the importance of involving all stakeholders for healthcare economics analysis for a more accurate cost estimation that would allow better planning of healthcare resources distribution and utilization of limited resources.⁵⁴

Acute stroke management

The management of acute stroke should start before the onset of stroke. Multiple reports derived from a study at Penang Hospital between January 2008 and June 2009, have shown that usage of HMG-CoA reductase inhibitors (or statins), angiotensin-converting enzyme inhibitors and antiplatelets, either alone or in combinations were associated with better functional outcome measured by Barthel Index on discharge, as well as significantly reduced in-patient mortality.⁵⁹⁻⁶² A sub-analysis on 295 diabetic patients reviewed that 38.3% of them were taking antiplatelet before index admission.⁶³ The main reason these patients were on antiplatelet was for previous stroke or ischemic heart disease. The data echoed the findings that better functional outcome upon discharge was observed among patients previously taking antiplatelet therapy.

Sahathevan R *et al.* reported a case of a 29-year old man presented with acute ischaemic stroke and received thrombolysis at 5.5 hours from the onset of symptoms, beyond the recommended onset-to-treatment time window of 4.5 hours, after careful consideration.⁶⁴ He had a small infarct core in the right lenticulostriate territory with a significant penumbra as evidenced from CTP images. He made good neurological recovery at two months.

Rasool *et al.* in their review stressed that the effect and safety of early lowering of blood pressure after intracranial haemorrhage has not been reliably examined.⁶⁵

There was a pilot study on 18 subjects with hemorrhagic stroke involving the induction of intravascular hypothermia within 48 hours after presentation.⁶⁶ The hypothermia was induced with an intravascular catheter placed over inferior vena cava at 34°C and maintained for 24 hours followed by gradual re-warming. Stroke severity measured by modified Rankin Scale (mRS) at 6 months and 1 year follow-up showed a significant improvement for patients receiving the study intervention.

In recent studies, comparison of recanalization success and clinical outcomes in acute ischemic stroke using intra-arterial therapy and intravenous tissue plasminogen activator have been inconsistent. Ramaiah SS *et al.* described the potential role of arterial collateralization assessment as a selection tool to identify suitable acute stroke candidates whom will likely to benefit from intra-arterial therapy.⁶⁷ This assessment focuses on leptomeningeal anastomoses, which composes of secondary network of cerebral collateral circulation besides the Circle of Willis.

The Chinese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study tested the investigational product MLC601 in patients with acute, moderately severe ischemic stroke presented within 72 hours from stroke onset.⁶⁸ MLC601 (NeuroAID) combines extracts of 9 herbal and 5 animal components in capsule form. At the end of 3 months, MLC601 was not statistically better than placebo in improving stroke severity and functional outcomes. But post hoc analysis showed that it was associated with reduced early vascular fatal and non-fatal composite outcomes such as recurrent stroke, acute coronary syndrome and vascular death at 3 months after index stroke.⁶⁹

In addition, prevention of acute post-stroke complications such as venous thrombosis, pressure ulcer, aspiration pneumonia and gastrointestinal bleed is important. In a six-month observational trial, the in-hospital stroke complication rate was 20.9%.²³ Stroke-associated infections such as pneumonia (12.3-15.8%), septicaemia (11.0%), urinary tract infection (3.7-4.3%) were the leading complications, followed by upper gastrointestinal bleeding (3.7-5.2%), recurrent stroke (3.1%), depression (2.5%), bed sores (1.2%) and deep vein thrombosis (0.6%).^{23,70-72} It was also demonstrated that MCA infarcts, diabetes, severe disability, poor Glasgow Coma Scale (GCS) independently predicted these post-stroke complications, which led to increased in-patient mortality. In another larger study involving 1,153 patients from 10 Asian countries which included Malaysia, complications occurring within 14 days of stroke included chest infections (9.4%), constipation (7.9%), urinary retention (5.0%), recurrent stroke (4.9%), urinary tract infections (4.9%), depression (4.0%), pressure sores (2.6%), aspiration (2.5%), falls (2.4%), upper gastrointestinal bleeding (1.6%), epileptic seizure (1.3%), arthritis (0.7%), deep vein thrombosis (0.5%), cardiac arrhythmias (0.3%), congestive heart failure (0.2%) and pulmonary embolism (0.1%).⁵³

Tan KS *et al.* performed a literature research on the available evidence of venous thromboembolism (VTE) among ischemic stroke patients in Asia and found a wide range of reported prevalence of VTE after stroke.⁷³ The prevalence of 1% was reported in clinical studies and 4.8% to 45% in imaging studies. These prevalence rates were lower compared to Western studies. However, the available literature involved only small sample size.⁷³

Stem cell therapy in the treatment of stroke is still at the experimental stage. Gopurappilly R *et al.* reviewed the latest success and future prospects of stem cell therapy.⁷⁴ Current works suggest that the earlier belief of stem cell mechanism of action via cell replacement may be incorrect. There are evidence that cell therapy works mainly by providing trophic support to the damaged neurons to foster neurogenesis and angiogenesis. The authors further emphasized the importance of continued preclinical work to understand better the mechanisms of action of stem cells.

Long term stroke management

Aznida FAA *et al.* conducted a survey among family medicine specialists using a semi structured self-administered questionnaires to evaluate practices in managing post-

discharge stroke patients at primary care setting.^{75,76} As high as 72.4% of the interviewed physicians did not have a standard care plan although about 96% would agree on the importance of having one to improve the quality of post-stroke care.⁷⁶ Apart from a standardized guideline, they also emphasized the needs of access to rehabilitative services, coordinated multidisciplinary care with tertiary centre and good family and caregiver support in strengthening stroke management in primary care.⁷⁶

Asian population has a slightly lower incidence and prevalence of AF than the Western population, but have a similar relative risk of stroke and mortality.⁷⁷ A lenient approach for long term control aiming for a ventricular rate of less than 110 bpm may be adequate. However, stricter rate control may be needed if patients continue to complain of symptoms. One review reported an AF prevalence of 2.8% among hospitalized patients in Malaysia and overall use of warfarin for AF was only 20%.²⁶

Warfarin resulted in an increased rate of hemorrhagic stroke in Asians compared to non-Asians in a controlled trial. Newer anticoagulation agent such as dabigatran etexilate posed a lower risk of major bleeding and hemorrhagic strokes compared to warfarin, and was consistent across Asian and non-Asian subgroups.⁷⁸ A retrospective observational study involving 510 patients attending the Malaysian National Heart Institute reported that usage of dabigatran in AF patients for stroke prevention had low rates of side effects (3.9% with dyspepsia) and bleeding (3.3% with minor bleeding and 0.4% with major bleeding).⁷⁹ Their median age was 68 years, median CHA₂DS₂-VASc was 2 and median HAS-BLED score was 2. None had ischaemic stroke, but one (0.2%) had haemorrhagic stroke, up to an average of 10-month follow-up.

Management of stroke should also target non-motor complications. Stroke survivors may suffer from dysphagia, which can lead to malnutrition and aspiration pneumonia. Those with moderate to severe dysphagia may require enteral tube feeding. A small prospective randomized trial involving 22 subjects comparing the effectiveness of percutaneous endoscopic gastrostomy (PEG) and nasogastric (NG) tube feeding found that PEG feeding had a modest but clinically significant improvement in serum albumin after 4 weeks of intervention, with a lower treatment failure.⁸⁰ Zaherah MSF *et al.* conducted a prospective study to examine the nutritional adequacy of patients on long term NG tube and to determine barriers to PEG feeding in these patients.⁸¹ They found that 64.3% on long term NG tube feeding had complications such as tube dislodgement (50.5%), aspiration of feed content (8.6%) and trauma from tube insertion (4.3%). Only half of the clinicians interviewed would routinely recommend PEG feeding, while 47.1% of the caregivers named 'lack of information' as the main reason of not opting for PEG feeding.

Stroke rehabilitation

In the past, it was believed that neurological improvement after stroke plateaued off after 6 months, hence cessation of rehabilitative services follows. A Cochrane review by Aziz NA *et al.* on the potential benefit of rehabilitation services for

patients after more than one year with stroke showed inconclusive evidence on the positive influence of the services to both patients' and carers' outcomes.⁸² Moreover, Aziz NA and Raymond AA in their review article stressed on the needs for longer-term stroke patients in the community.⁸³ Evidence showing improvement in stroke patient even after 1 year of stroke requires the healthcare managers to consider restructuring stroke rehabilitation beyond the first year of stroke and this service should encompass all aspects of patients' life.⁸³ Both rehabilitation professionals and stroke survivors expressed the needs for long term rehabilitation and recognized the barriers to such provision are multi-factorial.⁸⁴ Establishment of community-based rehabilitation centres and family-assisted home therapy were the potential strategies identified in the focused group discussion.

New innovative motivational community rehabilitation programmes were studied in RCTs. Subjects were allocated to two groups: the experimental group received 30 minutes of virtual reality balance games in addition to 90 minutes of standard physiotherapy while the control group received a total of 120 minutes of standard physiotherapy.⁸⁵ After 12 sessions of therapy, the outcome showed a significant improvement in Timed Up and Go test and the 30-second Sit to Stand test for the experimental group. There was however no difference in functional outcome measured using Barthel Index suggesting that this innovative method of physiotherapy could be an alternative to standard physiotherapy for stroke rehabilitation in community.⁸⁵ Another RCT assessed the effectiveness of digital videodisk containing therapy at home combined with twice monthly outpatient follow-up as compared to the conventional weekly outpatient therapy.⁸⁶ At 3 months, there was no difference in functional improvement, complication rates and Caregiver Strain Index among the two methods. This study suggested that video-based therapy at home for post-stroke rehabilitation is safe and did not increase caregiver stress, which can be an alternative for home care rehabilitation.⁸⁶

Aziz *et al.* looked into the outcome of community rehabilitation provided by primary care clinic in a prospective observational study.⁸⁷ The median interval between stroke event and point of first contact with the clinic for 91 patients was 4 months. It was shown that rehabilitation provided by primary care clinic had favorable outcome for blood pressure control (significant reduction in systolic blood pressure) and functional level (improved Barthel Index). There was also a trend of improvement but insignificant in depression scale measured by Patient Health Questionnaire (PHQ9).⁸⁷

Botulinum toxin is effective in reducing post-stroke spasticity. A RCT on 27 subjects showed that intramuscular injection of botulinum toxin A was safe and effective in the treatment of chronic post-stroke focal spasticity of the wrist and fingers, without serious treatment-related adverse effects.⁸⁸

Up to 70% of stroke patients reported the use of traditional complementary medicine as part of their rehabilitative care, such as acupuncture, massage and herbal medicine.⁸⁹ Recently, 17 post-stroke patients and 2 *urut Melayu* hospital

practitioners were interviewed for their experience and views on *urut Melayu* for stroke. This is a whole-body massage involving not only the body parts affected by stroke. Overall, *urut Melayu* gave the patients an unique and positive experience and were well-received.⁹⁰ A case report has described a 32-year old woman, following postpartum haemorrhagic stroke which rendered her bed-bound, had progressively improved speech and fine motor skills after 14 sessions of *urut Melayu*.⁹¹

On the other hand, Home Care Nursing Program designed by a university hospital did not show difference in terms of functional improvement outcome in post-stroke rehabilitation when compared to the routine therapy.⁸⁹ While this raises concerns on the efficacy of such programme, the small sample size and lack of clarity on the programme information might have affected interpretation on the study outcomes.

Yakub F and colleagues provided an interesting review on the current development of rehabilitative robotics as a promising tool for stroke rehabilitation.⁹² Besides, Abdullah MZ *et al.* described the potential use of brain-computer interface (BCI) technology in stroke rehabilitation.⁹³ The BCI is a computer-aided apparatus which decodes brain electrical activities and translates them to signals for activating external devices. It provides communication interface which can match with a stroke patient's residual motor disabilities to facilitate robotic-assisted rehabilitation. Recent experiment on stroke survivors suggested that BCI promotes cortical plasticity which allows the brain to re-organize around damaged cortical areas, hence recovering the functions of these areas.⁹³

Stroke outcomes for survivors and care-givers

Mortality and morbidity

In Malaysia, mortality due to stroke constituted 8.9% and 12.1% of total certified death for males and females, respectively.⁹⁴ The estimates of age-standardized stroke mortality were 103 per 100,000 males and 97 per 100,000 females.⁶

Stroke mortality varied widely between different studies, ranging from 3.3% to 37%.^{7,13,15-18} In the late 1990s, a prospective observational study in a tertiary centre in Kelantan revealed a 30-day mortality among first-ever stroke patients of 34%, with two-third occurred as in-patients,¹³ while in Penang Hospital it was 20.3%.¹⁴ Patients with haemorrhagic stroke had a higher mortality rate (27.3-36.8%) than those with ischaemic stroke (10.1-11.7%).^{15,16} Death occurred at a mean of 8 days after admission for ischaemic stroke and 3.8 days for haemorrhagic stroke.

Morbidity associated with stroke poses substantial burden to patients, their caregivers, healthcare systems and providers. The main contribution to morbidity is functional disability. In a prospective observational study, at discharge, only 13% of post-stroke patients were able to ambulate with aids and 87% needed assistance for ambulation of varying degree.⁹⁵ At 3 months, 82% showed improvement in overall function, 60% were ambulating independently with the remaining 40% still required assistance.

Manaf H *et al.* explained the post-stroke sensorimotor and balance dysfunctions and how they affect the mobility of stroke survivors when performing daily functions which require substantial walking coordination.⁹⁶ However, they concluded the lack of studies in understanding dual-task ability (motor and cognitive) on stroke patients, and proceeded to conduct two studies on this domain. They found that gait performance among stroke patients was compromised during dual-task conditions and recommended to incorporate attentional loading into routine gait assessment and rehabilitation.⁹⁷ Besides, they demonstrated that functional balance might be an influential domain in successful dual-task Timed Up and Go test.⁹⁸

Other post-stroke disabilities include dysphagia,^{80,99} emotion recognition deficit,¹⁰⁰ dementia^{101,102} and sleep-disordered breathing (SDB).¹⁰³ In a single centre observational study, as high as 41% of stroke patients experienced dysphagia at initial presentation and was reduced to 21.6% at one-month after index stroke.⁹⁹ Age ≥ 75 years (OR=5.20), diabetes (OR=2.91) and MCA infarct (OR=2.48) independently predicted the occurrence of dysphagia after an acute stroke.⁹⁹ In a more recent study, the prevalence of dysphagia was reported lower at 15.8%.¹⁰⁴

Yuvaraj R *et al.* discussed the problems of diminished ability to recognize emotions in post-stroke patients.¹⁰⁰ The extent of emotion recognition deficit appears to be correlated with interpersonal difficulties such as complaints of frustration, desire to attach with another person, feelings of social discomfort and use of controlling behaviours.¹⁰⁰ Such deficits were more frequently observed in individuals with right brain damage compared to those with left brain damage.

Stroke causes dementia and vascular risk factors appear to be independent risk factors for dementia. Hence, cognitive assessment must be included in post-stroke care. The Malay version of Montreal Cognitive Assessment (MoCA) had been validated for use in local stroke population.¹⁰⁵ Al-Qazzaz NK *et al.* reviewed the available neuropsychological assessments and proposed a post-stroke memory assessment (PSMA) as a tool for evaluating impairment of different memory functionalities (working, short and long term memories) and their severity.^{106,107} It may also detect the earliest stages of dementia before significant mental decline in post-stroke patients.¹⁰⁶ Sahathevan R *et al.* reinforced that risk factors such as hypertension, diabetes and dyslipidemia are independently associated with the increased risk of Alzheimer's dementia and vascular cognitive impairment.¹⁰² However, the mechanism of cardiovascular risk factors affecting Alzheimer's dementia remains largely unknown. Stroke patients aged ≥ 65 years were prone to have cognitive impairment.¹⁰⁸ This study also illustrated that cognitive impairment among stroke patients had significant relationship with general health status, depression, activities of daily living, overall social and family support.

Prevalence of SDB was reported at 78.5% with a cut-off of apnoea-hypopnoea index ≥ 10 in a study involving 28 acute ischemic stroke patients.¹⁰³ Diabetes and smoking history were the significant predictors for post-stroke SDB.

Mood disorders such as depression,¹⁰⁹⁻¹¹¹ mania¹¹² and bipolar disorders,¹¹³ often received limited attention in stroke care process. Other rarer complications include emotional incontinence^{114,115} and complex regional pain syndrome¹¹⁶ have been described.

The prevalence of depression was as high as 36% between 4 to 8 weeks after stroke, using the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) criteria.¹¹⁰ Depression was associated with left hemisphere brain lesion, physical disability measured by mRS >2 and previous history of depression.¹¹⁰ Glamcevski *et al.* had reported even higher prevalence of depression (66%) at 3 to 6 months after stroke, whereby 51% having mild depression and the remaining 15% with moderate to severe depression.¹⁰⁹ In the same study, depression was higher in both Malay and Chinese ethnic groups than the Indians. Other significant factors included age, discontinuation of pre-stroke lifestyles and poor performance in the activities of daily living.¹⁰⁹ The prevalence of depression was also comparable to stroke patients with vascular dementia at 31.6%.¹¹¹ Patients in this subgroup who were older, suffered large artery stroke or right-sided large artery stroke, lower Mini Mental State Examination score and lower Barthel Index were more likely to suffer from depression.

On the other hand, patients with stroke affecting the right cerebral hemisphere or limbic structures may present with the other extreme of mood disorders. A 72 year-old lady presented with abnormal increased goal-directed behaviour associated with visual and auditory hallucinations had a right MCA territory infarct.¹¹² Tan EC *et al.* reported a case of multifocal cerebral infarcts with right thalamic bleed and illustrated that post-stroke mania and psychosis could potentially due to either the stroke process itself, underlying bipolar disorder or a side-effect of medication.¹¹⁷ In this report, amitriptyline could have contributed to the development of neuropsychiatric manifestations. Post-stroke mania, however, is a very rare phenomenon. Two other reports described post-stroke emotional incontinence, where patients have heightened tendency to cry or laugh, out of the proportion of their underlying mood as a sequelae of brain damage.^{114,115} An interesting case report described a previously healthy 15-year old teenage girl presented with sudden onset of right-sided weakness and subsequently developed alternating depressive and manic symptoms, who was later diagnosed of having bipolar mood disorder secondary to mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS).¹¹³ Her brain MRI showed multifocal enhancing lesions in bilateral basal ganglia, internal capsules and brainstem.

Quality of life

In a study by Nor Azlin *et al.*, mean score for all eight health domains in the Short-Form Health Survey (SF-36) among stroke patients was lower compared to the general population, except bodily pain.¹¹⁸ Female subjects reported higher score in all domains compared to men, especially in general health and social functioning domains.¹¹⁸ The health-related quality of life was not affected by post-stroke duration in this study. Similar findings were reported by Samsiah *et al.* using a different measuring tool for quality of

life, namely Stroke Specific Quality of Life (SS-QOL).¹¹⁹ This cross-sectional study conducted on 107 post-stroke patients revealed that their mean SS-QOL was 141.8±40.32. The two domains affected were work and productivity, as well as thinking. However, few items from SS-QOL were inappropriate in developing country and not culturally sensitive.

Caregivers of stroke survivors

Fatimang L *et al.* investigated the stroke care burden among 96 women caring for elderly stroke survivors and factors influencing it. Using Zarit Burden Interview short version to measure care burden, more than one-third of them perceived of having high burden as caregivers.¹²⁰ Factors associated with high care burden included caring for stroke patients who were bed bound and duration of daily care duty of ≥8 hours.

Predictors of stroke-associated disability and survival

A prospective study on 218 patients has identified several independent predictors of in-hospital mortality for acute ischemic stroke patients, such as MCA infarct (OR=1.21), AF (OR=9.77), diabetes (OR=4.88), Barthel Index <5/20 (OR=4.2) and GCS <9 (OR=3.9), regardless of age and gender.¹⁵ Another study demonstrated GCS deterioration (OR=46.04), poor GCS on admission (OR=12.35) and haemorrhagic stroke (OR=3.45) being the independent predictors of one-month mortality for stroke patients.¹⁴ Besides, dysphagia at initial presentation has been shown to be an independent predictor for stroke-associated mortality during hospitalization¹⁶ and at one-month.⁹⁹ Diabetes with high blood glucose level on admission (OR=4.88) was also a significant predictor of mortality.²⁰ Stroke patients with AF had longer hospital stay, higher mortality rate and greater functional disability upon discharge, compared to patients without AF.²²

High blood pressure after intracranial hemorrhage may have detrimental outcome, possibly contributing to complications such as re-bleeding and hematoma expansion.⁶⁵ Patient who developed stroke-associated pneumonia (OR=14.90) had significant shorter mean survival compared to patients who did not.⁷²

In a prospective observational study involving 79 subjects, fewer stroke patients with BMI ≥25kg/m² had severe disability (mRS=5) at 1 month compared to their counterparts with BMI <25kg/m².¹²¹ However, multivariate analysis did not support BMI being an independent predictor for stroke severity in this study, besides the patient's age.

Leukoaraiosis or white matter abnormality was present in 48% among a small cohort of 60 acute stroke patients admitted to a tertiary university hospital.¹²² Such abnormality correlated significantly with aging and hypertension. Its presence did not affect functional disability (Barthel Index was <60) and mortality at three months post-stroke, but could predict early cognitive dysfunction.

The role of biomarkers in predicting stroke outcome remained equivocal. Plasma for tissue factor (thromboplastin) did not correlate with physical functionality at one month post stroke and recurrent stroke event.¹²³ However, age and MCA infarcts were significant independent predictors for severe disability with Barthel Index ≤9 at one month. On the other hand,

elevated C-reactive protein (CRP) within 72 hours after an acute ischaemic stroke was significantly associated with poorer physical functional outcome at one month and predicted a larger infarct size.¹²⁴ It was hypothesized that CRP elevation may reflect the extent of ischaemic area while post-ischaemic inflammation may contribute to continuing ischaemic brain injury.

SECTION 4: FUTURE RESEARCH DIRECTION FOR STROKE IN MALAYSIA

Stroke is a leading cause of adult disability and dependency, resulting in substantial demands in individual, family and healthcare resources in the country. There are many challenges in stroke research closely related to socioeconomic, political and regulatory factors. Nonetheless, there are growing potential areas for epidemiological, clinical, genetic, psychosocial and economic research in stroke, given the quantity and diversity of patients in Malaysia.¹²⁵

There were only two large epidemiological studies comparing of the disease burden with neighbouring ASEAN countries.^{4,6} The majority of the prospective studies looking at stroke outcomes mainly focused on mortality and morbidity, with their associated predictors, and were of single centre experience. Further research comparing the vital registries of the population (mortality) and those reported from NSR, as well as head-to-head comparisons with other developing and developed countries will depict a clearer picture of stroke burden in Malaysia and to understand the gaps in stroke services in the country. Epidemiological research on ethnographic propensity for stroke, factors contributing to recurrent strokes, issues pertinent to cardioembolic stroke are in need. The National Stroke Registry could be improved with mandatory updates from all regional hospitals, and increasing financial and logistical supports from the government.¹²⁶

With regards to risk factors for stroke, there were few single centre studies looking at risk factors associated with acute ischemic stroke. Few case reports have described rare causes of stroke. Data on common risk factors management and stroke incidence are lacking. Studies on post-stroke risk factors control and outcomes will help to identify areas for improvement in stroke care. Besides, the increasing young stroke and haemorrhagic stroke with their associated risk factors are yet to be further explored.

There have been growing interests in identifying potential biomarkers (fibrinolytic markers, microRNA profiling, tissue factor, CRP, homocysteine with specific genotype), which might prognosticate the disease. However, these studies with small sample size might have led to inconclusive results. There was a small prospective observational assessing the role of CT perfusion scan, in identifying hyperacute stroke, to guide thrombolysis therapy. Review articles on ASPECTS score and assessment of arterial collateralization will be of interest for clinicians in pursuit of advancement in this field.^{45,67} Further research require larger sample size and to assess the feasibility and applicability of these diagnostics and prognostics tools at the local settings.

There has been encouraging involvement of Malaysian researchers, and Malaysian patients in RCTs for acute and post-stroke interventions at both local and international settings. Although local RCTs were of small sample size, the results were encouraging. For instances, intravascular hypothermia might have beneficial effect in acute haemorrhagic stroke, PEG-tube feeding improved nutritional status with reduced complications compared to NG tube feeding, and botox injection was beneficial for post-stroke wrist and finger spasm. Some observational studies demonstrated the beneficial roles of statins, ACEi, antiplatelet or combination in improving stroke mortality. While the review articles on robotically assisted brain controlled interface and stem cell therapy for neuro-regeneration are interesting, field studies are yet to be conducted. Given the magnitude of the disease burden and emerging treatment modalities, many more hypotheses can be tested through RCTs. In the coming years, more local data on outcomes of thrombolytic therapy will be reported, as the study is currently undergoing.

With the growing prevalence of stroke over time, the burden of post-stroke complications, particularly depression and dementia, poses threats to the already overwhelmed healthcare system, not to mention the strains on the psychosocial aspects of patients and their caregivers. In fact, these long term complications are not routinely addressed in clinical practice during long term follow-up. Continuous surveillance and effective screen-to-treat strategies should be designed and incorporated into the integrated stroke care pathways.

Rehabilitation is a vital component in stroke care. Innovative home-based therapies as an alternative to standard physiotherapy have been studied. However, their feasibility and applicability to the larger affected population remain unknown. There is a need to assess the readiness of community services to handle growing stroke patients, to map the healthcare facility such as rehabilitation centre, to the needs of the population. While primary care services are “well” designed for managing majority of non-communicable diseases, it is rather a fragmented one for stroke, due to the lack of coordination and organized care pathway for patients. Besides, the potential roles of traditional complementary medicine as an adjunct rehabilitative are to be further explored.

There have been attempts to study the healthcare cost for managing stroke patients. Undoubtedly, there is a great need to evaluate the cost of stroke not only to the healthcare sector which involves acute admission, complications and management, recurrent admissions and long term follow-up, but also to the society at large. The latter should include DALYs, all the indirect costs incur to patients and care-givers.

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A Review of Lung Cancer Research in Malaysia

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ABSTRACT

Lung cancer is a major cause of mortality and morbidity in Malaysia and worldwide. This paper reviews all research and publications on lung cancer in Malaysia published between 2000-2015. 89 papers were identified, of which 64 papers were selected and reviewed on the basis of their relevance to the review. The epidemiology, risk factors, cell types, clinical presentation, diagnosis, treatment, outcomes, prevention, and the social impact of lung cancer in the country are reviewed and summarized. The clinical relevance of the studies done in the country are discussed along with recommendations for future research.

KEY WORDS:

Lung cancer; lung carcinoma; lung neoplasm

INTRODUCTION

Lung cancer is the leading cause of cancer related deaths worldwide with 30-40% occurring in developing countries.¹ In 2012, there were more than 1.8 million lung cancer diagnoses worldwide causing 1.6 million deaths. The incidence of lung cancer and consequent death from this disease is anticipated to increase over the next decade due to the high rates of smoking.²

This review covers all studies on lung cancer done in Malaysia. A review of research done in the country on lung cancer is important as results reported worldwide, particularly in Western developed countries, may not necessarily be the same in a developing Asian country. A literature search of articles as detailed in the paper "Bibliography of clinical research in Malaysia: methods and brief results" covering the years 2000-2015 was undertaken. The PubMed search involved the medical subject heading (MeSH) "lung neoplasm". 89 papers were identified of which 64 were selected for their relevance.³

SECTION 1: REVIEW OF THE LITERATURE

EPIDEMIOLOGY

Incidence and prevalence

According to the 2014 World Health Organization report, lung cancer accounted for 19.1 deaths per 100,000 population in Malaysia or 4,088 deaths per year (3.22% of all deaths), the second most common cause of death due to cancer in the country after breast cancer, and the eighth most common cause of death from all causes. In 2014, cancer of the trachea, bronchus and lung accounted for 24.6% of all cancer mortality in males in the country, the most common

cancer death, while in females, it accounted for 13% of all cancer deaths, the second most common cancer death after breast cancer. 4,403 lung cancers were diagnosed in the country in 2014, 3,240 in males (the most common cancer diagnosed), and 1,163 in females (the fourth most common cancer diagnosed).

Information on the epidemiology of lung cancer was also obtained from the National Cancer Registry (NCR). From its last published report in 2007, lung cancer was the third most common cancer in the country, the second most common cancer in males and the 4th most common in females.⁴

Age

The mean age at which lung cancer is diagnosed in Malaysia is about 60 years with a peak age of diagnosis in the 7th decade. The incidence of diagnosed lung cancer in Malaysian patients aged less than 40 years is relatively low at approximately 6.2%.⁵ Younger patients were more likely than older patients to have adenocarcinoma with poorer World Health Organization (WHO) performance status.⁶ Late stage presentation and therefore inoperability is very common in the younger age groups as they usually remain asymptomatic or ignore symptoms longer. In one study, all patients less than 40 years old with non small cell lung cancer (NSCLC) presented with either stage IIIb or metastatic disease, compared to 77% of older patients ($p < 0.001$).⁶

Ethnicity

There was an over representation of Chinese among patients with lung cancer. The ethnic distribution was similar for the younger and older groups of lung cancer patients. (Chinese 71%, Malay 19%, Indian 9%, others 1%, $p < 0.001$).^{5,6} The age-standardized incidence of lung cancer amongst the Chinese is two-fold that of non-Chinese. The precise reason for this observation is uncertain but smoking volume and a genetic predisposition to cancer may be partly responsible.⁷

Primary lung cancer

Historically, squamous cell carcinoma was the commonest lung cancer cell type. However, over the years, adenocarcinoma has now replaced squamous cell carcinoma as the commonest lung cancer cell type (Table I). The reason for this shift of cell type is unknown. Possible reasons include diagnostic advances, switch of smoking from high-tar to low-tar filtered cigarettes and changes in smoking patterns.⁵

An eight-year retrospective study done at University of Malaya Medical Center revealed adenocarcinoma subtype as the most common cell type in all age groups with a

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Table I: Histological Subtypes of lung cancer in different institution in Malaysia

Author (ref)	Institutions	Sample Size (n)	Adenocarcinoma (%)	Squamous Cell (%)	Large Cell (%)	Poor or no Differentiation (%)	Small Cell (%)	Other (%)
C-K Liam <i>et al</i>	UMMC (1991-1999)	580	252 (43.4)	165 (28.4)	19 (3.3)	70 (12.1)	69 (11.9)	5 (0.9)
S.H How <i>et al</i>	UMMC (Sept 1994 – Aug 2002)	503	206 (40.9)	153 (30.4)	14 (2.8)	65 (12.9)	65 (12.9)	-
A R M Fauzi <i>et al</i>	Hospital Sultanah Aminah (Jan 1997 – Dec 1999)	236	66 (28.0)	73 (30.9)	19 (8.1)	28 (11.9)	45 (19.0)	5 (2.1)
Catherine MM <i>et al</i>	UMMC (Mac 1998 – Oct 1999)	50	19 (38.0)	17 (34.0)	-	-	5 (10.0)	7 (14.0)
L-C Koh <i>et al</i>	Seremban Hospital & Nilai Cancer Institute (Jan 1996 – Apr 2004)	119	35 (29.4)	55 (46.2)	8 (6.7)	-	-	21 (17.6)
S.H How <i>et al</i>	UMMC (May 2001 – Jan 2002)	24	15 (62.5)	4 (16.7)	3 (12.5)		2 (8.3)	-
T.H. Ng <i>et al</i>	HTAA§ (Nov 2007 – Nov 2009)	95	88 (92.6)				4 (4.2)	3 (3.2)
S H How <i>et al</i>	HTAA (Aug 2007 – Aug 2010)	149	78 (52.3)	28 (18.8)	1 (0.7)	21 (14.1)	6 (4.0)	6 (4.0)
C-K Liam <i>et al</i>	UMMC & HTAA (Aug 2010 – Dec 2011)	151	131 (86.8)	11 (7.3)	1 (0.7)	-	-	1 (0.7)
N.S.Y Tiffany <i>et al</i>	Sime Darby Medical Center (Jan 2011 – Apr 2012)	484	467 (96.5)	12 (2.5)	3 (0.6)	-	-	2 (0.4)

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Table II: Stage at presentation of lung cancer in different institutions in Malaysia

Author (ref)	Institutions	Sample Size (n)	Stage Ia (%)	Stage Ib (%)	Stage IIa (%)	Stage IIb (%)	Stage IIIa (%)	Stage IIIb (%)	Stage IV (%)
C-K Liam <i>et al</i>	UMMC (1991-1999)	510	16 (31.3)	35 (68.6)	2 (0.4)	15 (2.9)	41 (8.0)	186 (36.5)	215 (42.2)
L.N Hooi <i>et al</i>	Penang GH (1995 – 2001)	67	35 (52.2)		16 (23.9)		16 (23.9)		-
L-C Koh <i>et al</i>	Seremban Hospital & Nilai Cancer Institute (Jan 1996 – Apr 2004)	119	8 (6.7)				111 (93.3)		
Bassam Abd Rasool Hassan <i>et al</i>	Penang General Hospital (2003 – 2009)	118	11 (6.9)		25 (21.2)		47 (39.8)		29 (24.6)
T.H. Ng <i>et al</i>	HTAA (Nov 2007 – Nov 2009)	95	-	-	-	-	3 (3.2)	50 (51.6)	43 (45.2)
S H How <i>et al</i>	HTAA (Aug 2007 – Aug 2010)	149	-	-	-	-	5 (3.4)	76 (51%)	68 (45.6)
C-K Liam <i>et al</i>	UMMC & HTAA (Aug 2010 – Dec 2011)	151	4 (2.6)	4 (2.6)	2 (1.3)	2 (1.3)	7 (4.6)	9 (6.0)	123 (81.5)

comparatively higher incidence in the younger patient less than 40 years old 24/36 (77.7%) vs 228/544 (41.9%); $p < 0.001$; younger patients were less likely to develop squamous cell carcinoma ($p = 0.047$).⁶ Another study done by the same group revealed that the percentage of patients diagnosed with adenocarcinoma increased from 25% during the period 1967–1976 to 43% during the period 1991–1999 with a corresponding drop in the incidence of large cell carcinoma from 12% to 3%. There was no significant shift in the incidence of squamous cell carcinoma.⁵ Small cell lung cancer (SCLC) accounted for about 12% of all lung cancer cases. In recent years, the incidence of SCLC seems to be on the decline. Two-thirds of cases of SCLC are diagnosed with advanced stage disease.⁵

Several rare lung tumours were reported in Malaysia. Clear cell tumours of the lung are rare type of primary lung neoplasm. Shiran and colleague reported a case of clear cell “sugar” tumour of the lung. Although the majority of clear cell tumours follow a benign course, there are reported cases of malignant features such as lymphovascular invasion, necrosis and pleomorphism.⁸ Primitive Neuroectodermal Tumours (PNETs), a type of aggressive tumour arising from mutation of the pluripotent neural crest cells, typically occur in the bone and soft tissues and rarely present as an organ-based neoplasm. Primary lung PNETs may rarely occur but involvement of the heart as the site of metastasis is even rarer. Harris, *et al* reported a rare case of pulmonary PNETs with pericardial involvement.⁹

Multiple primary malignancies involving the lung are extremely rare. Iqbal, et al published a case report describing a patient with three simultaneous primary cancers: in the larynx (well differentiated squamous cell carcinoma), lung (non-small cell carcinoma) and thyroid (sclerosing papillary carcinoma).¹⁰

Secondary lung cancer

The common primary sites of metastasis to the lung are from the colon, breast and bone. In one study, the median survival for patients with lung metastasis from primary breast cancer was found to be 24 months.¹¹ A retrospective review of medical records in 31 patients diagnosed with giant cell tumour of the bone in University Malaya reported that 4 patients developed pulmonary metastasis.¹² A similar study conducted by Faisham, et al revealed that 6 out of 24 patients with giant cell tumour of the bone had pulmonary metastasis. 2 patients with resectable disease were treated with surgical resection, 2 were treated with chemotherapy and the disease remained non progressive, while the remaining 2 patients refused chemotherapy (in which one of them succumbed to the disease due to massive hemoptysis). The study concluded that aggressive treatment of pulmonary metastases in patients with aggressive giant cell tumour of the bone is mandatory for overall prognosis.¹³

Tumour size reflects tumour burden and/or the extent of disease. A retrospective data review conducted at Universiti Sains Malaysia studied the association between tumour volume and the occurrence of lung metastasis in patients with osteosarcoma. 47% of the 70 patients with osteosarcoma studied had evidence of lung metastasis. Tumour volume was directly associated with occurrence of lung metastasis ($p=0.048$). The proportion having lung metastasis when the primary tumour volume exceeded 371 cm³ was 69% compared to 34% in smaller tumours. An increase in tumour volume represented an increase in the probability of lung metastasis with a positive predictive value of 69%.¹⁴

PUBLIC KNOWLEDGE AND AWARENESS

A cross-sectional study on lung cancer awareness was conducted by Al-Naggar, et al in 2012, involving 150 secondary school teachers randomly chosen from three different secondary schools in the Kudat district, Sabah. The overall knowledge on lung cancer was found to be low.⁵¹ More than half the secondary school male teachers (57%) thought that only males are affected by lung cancer, and 71% thought that lung cancer can be transmitted from person to person.⁵¹ Knowledge on the risk factor for lung cancer was better with 91% of participants aware that cigarette smoking is the main risk factors for lung cancer.⁵¹ Similar results were observed in another similar study involving 213 university students, which revealed that 100% of the participants were aware that smoking is the main risk factor for lung cancer, and 90% were aware of passive smoking as a risk factor.⁵²

PREVENTION

According to the National Health and Morbidity Survey (III) conducted in 2006, the prevalence of smokers in Malaysia was 27%. However, it is noteworthy that a significant

proportion of people who develop lung cancer in Malaysia are life-long non-smokers.⁴⁸ The percentage of male patients with lung cancer who were smokers increased significantly from 86% in 1967–1976 to 92% in 1991–1999.⁵ The percentage of people with lung cancer who had never smoked was higher among the younger patients (58% vs 19%, $p<0.001$).⁶ This is in contrary to the Western populations, in which younger lung cancer patients are more likely to have been smokers. However, data regarding the intensity of smoking was not available in 17% of the patients studied.⁶ Another single institution prospective study done by Catherine et al, support the fact that smoking was more common in older patients (60 years and above) ($p=0.002$) and there were significantly more smokers in the older patients who had carcinoma. The subanalysis of the same study also revealed that the older age group smokers averaged 67.7 (range 20–120) pack-years, while the younger smokers averaged 29.3 (range 10–92) pack-years.¹⁵ Adenocarcinoma and squamous cell carcinoma were both significantly less strongly associated with cigarette smoking in the younger than in the older patients. ($p<0.001$ and $p=0.027$ respectively). A high percentage of non-smoking female patients with adenocarcinoma and a younger age of diagnosis of adenocarcinoma suggest that risk factors other than active smoking may be involved in carcinogenesis in these patients.⁴⁹

CLINICAL PRESENTATION

Clinical symptoms suggestive of lung cancer include cough, hemoptysis, weight loss and chest pain. A cohort study of 160 patients done at a University Hospital showed that the main cause of haemoptysis in older patients (60 years old and above) was bronchogenic carcinoma (49%).¹⁵ The majority of bronchogenic carcinoma in this study was located in the proximal airways.¹⁵

Pleural effusions were found to be a common sign of lung cancer. In a retrospective study of 189 patients with mean age 51.2 years, malignancy ranked as the second most common cause of exudative pleural effusions (30%) after tuberculosis. 95% of malignant pleural effusions were due to primary lung cancer.¹⁶ Another prospective study done in the same institution 3 years later by How, et al, revealed that neoplastic pleural effusions was more common than that due to tuberculosis (34% versus 23%).¹⁷ The histological diagnosis of malignant pleural effusion was made by bronchoscopic biopsy in 66% of cases, by pleural fluid cytology in 59%, and by pleural biopsy in 50%. The combination of these three procedures significantly increased the diagnostic yield to 96%.¹⁷ Malignant effusions were found to be more frequent among patients older than 50 years (75%) and were likely to be large at presentation.¹⁶

Clinical symptoms and signs due to Cushing's disease may be associated with pulmonary carcinoid tumour with ectopic ACTH production and its precursors. Wong, et al reported a rare case of ectopic ACTH-producing atypical carcinoid associated with a non-functioning pituitary macroadenoma, which is strongly associated with multiple endocrine neoplasia (MEN) type 1.¹⁸ In a rare condition known as Masquerade Syndrome, there is a presence of an ocular

involvement of lung cancer. Pathology involves exudative type retinal detachment which is manifested as sudden and progressive loss of visual field and reduction in visual acuity. Kalthum, *et al* reported a rare case of Masquerade Syndrome secondary to poorly differentiated adenocarcinoma of the lung in a 37 year-old gentleman.¹⁹

MANAGEMENT

Diagnosis

In Malaysia, most lung cancer cases are diagnosed late with either locally advanced disease or distant metastasis (Table II). 75-88% of lung cancer cases are diagnosed in stage III or IV; these patients can only be offered palliative therapy.⁵ Only about 12% of cases present early enough to be offered curative surgical resection.⁴

Loh, *et al*, studied the time to diagnosis of lung cancer from clinical presentation. Significant delay is present in the diagnosis of lung cancer with the median patient-delay being 60 days (range 30–150 days) and the median doctor-delay being 33 days (range 18–72 days).²⁰ Reasons for the delay in diagnosis of lung cancer include the failure to recognize symptoms and patient beliefs in traditional complementary medicine.²⁰

Following an abnormal CXR, bronchoscopy was diagnostic of lung cancer in 54% of older patients versus 33% in younger patients ($p=0.005$). Bronchoscopy alone or combined with CT of the thorax achieved the highest yield of diagnosis regardless of the age group and was significantly more diagnostic in older patients (60 years and above).¹⁵ Liam, *et al* carried out a retrospective analysis on 503 patients with confirmed lung cancer to determine if the diagnostic yield of flexible bronchoscopy was dependent on tumour location. Bronchoscopy sampling procedures involved several techniques including bronchial washing (BW), bronchial brushing (BB), broncho-alveolar lavage (BAL), transbronchial biopsy (TBB) and endobronchial biopsy (EBB). BW followed by EBB and then BB were performed sequentially for patients with bronchoscopically visible tumours. For patients with tumours which were not visible by bronchoscopy, BAL was performed first, then BB, followed by TBB. EBB was reported to be less likely to be diagnostic in patients with tumours in the middle or lingular lobe bronchi. The diagnostic yield of all the other sampling techniques were not influenced by the location of the tumours or tumour visibility by bronchoscopy.²¹ Overall, the diagnostic yield of bronchoscopy sampling in this study was 71%.²¹ Lung cancer lesions were most frequently located in the upper lobe (47.5%). Lesions in the upper lobes are often technically difficult to access because of the acute angulation of the bronchoscope needed to reach them. Squamous cell carcinoma and small cell lung carcinoma were more commonly associated with bronchoscopically visible tumours compared to the other cell types.²¹ In another retrospective study of all bronchoscopy records for investigation of lung cancer at Hospital Sultanah Aminah, Johor Bahru, the addition of cytological specimens from BB and BW to EBB significantly increased the diagnostic yield by 17% (22/59 to 32/59) when no mass lesion was visible bronchoscopically. When endobronchial lesions were visible, the addition of

cytology specimens to endobronchial biopsy produced only a small insignificant increase in the positive result for cancer and was not cost effective.²² The authors concluded that routine cytological specimen collection by BB and BW in cases of visible endobronchial lesions during bronchoscopy had low additional value and should be discouraged.

Transbronchial needle aspiration (TNBA) is another valuable tool to diagnose lesions in the mediastinum and lung without subjecting the patient to surgical biopsy.²¹ This technique is used to sample either suspected lesions or enlarged paratracheal and subcarinal lymph nodes identified by CT scanning. A retrospective review of patients undergoing TNBA at Hospital Tengku Ampuan Afzan reported a success rate of 60% in yielding histological diagnosis.²³ TBNA is particularly useful in establishing histological diagnosis in patients with peripheral lung lesions, mediastinal lymphadenopathy (for staging or diagnosis), and drainage of mediastinal cyst or abscess.²³ However, the technique is operator-dependent, and also dependent on other factors to achieve high yield, including type of needle used, technique, CT evaluation, tissue preparation and interpretation, as well as nodal site and size.²³ Conventional TNBA is gradually being superseded by endobronchial or endoscopic ultrasound guided TNBA, which was reported to give a diagnostic yield as high as 90%, and has been shown to reduce the need for surgical staging.²⁴

A case study done by Gita, *et al*, reported a successful diagnosis of a colloid carcinoma or mucinous carcinoma of the lung (a subtype of peripheral lung adenocarcinoma) with CT-guided transthoracic-FNA. Cytological diagnosis of colloid carcinoma is extremely difficult owing to the paucity of tumour cells relative to the amount of mucin present.²⁵

Sanchithanandan, *et al* reported a rare case of two synchronous primary non-small cell lung cancers (NSCLC) diagnosed post-operatively following pathological examination of the resected lobe using immunohistochemistry markers (IHC); TTF-1 and the epithelial marker CK-7 are highly sensitive and specific for a primary NSCLC and non-reactive for metastatic lung adenocarcinomas.²⁶

Biomarkers

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein encoded by a gene located at the short arm of chromosome 7; it functions to stimulate a wide range of cellular functions such as cell proliferation, differentiation, migration and survival. Specific mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR) are associated with improved responses in NSCLC patients receiving EGFR-targeting tyrosine kinase inhibitors (TKIs).

In Malaysian patients with NSCLC, the EGFR mutation rate was found to be similar to that in other Asian populations but higher compared to Western populations.²⁷ In a study conducted by Tiffany, *et al*, all of the EGFR mutations were found in adenocarcinoma tumours except one that was in squamous cell carcinoma. The mutation rate was 46% (221/484) and was more frequent in women (61%, $p<0.001$).²⁸

Similar results were observed in a retrospective study done on patients from 44 private and public hospitals between 2009 and 2011 where 40% of tumours from 812 patients with advanced adenocarcinoma were EGFR mutation positive.²⁹ In a study by Liam, *et al*, EGFR mutations were significantly more frequent among females (53% vs 28%, $p<0.001$) and in non-smokers (55% vs 21%, $p<0.001$). Non-smoking status was the only independent predictor of EGFR mutation positivity (OR: 3.82, $p=0.002$). These observations may suggest some association with preferential occurrence of EGFR mutations in non-smoking women.²⁹ Most EGFR mutations involved deletions in exon 19 and 21 (24% and 19% respectively) and were significantly more common in females ($p<0.001$). Exon 19 deletions in tumours tended to occur in younger patients (mean age 57.4 years) compared to exon 21 deletions (mean age 65.1 years), a mean difference of 7.8 years.²⁷ Complex mutations were also observed, where 8 tumours carried 2 mutations and 1 tumour carried 3 mutations.

Direct sequencing is considered the “gold standard” in nucleic acids studies, but its use was limited due to low sensitivity, high cost and long turnaround time. High resolution melting (HRM) and Scorpion amplification refractory mutation system (ARMS) are emerging techniques for rapid detection of DNA sequence variation. Both methods were found to be useful for detection of EGFR mutations; all mutations identified by ARMS in one study were correctly matched in HRM analysis.²⁸ The detection of EGFR mutation-positive tumours by Scorpion ARMS was comparable to that by direct sequencing in one study (170 of 396 tumours or 42.9% compared to 151 of 416 tumours or 36.3%).²⁹

TREATMENT AND OUTCOMES

Surgical resection

The most effective option for treatment of lung cancer is surgical resection, when feasible. However, most patients with lung cancer do not undergo surgical resection; in a single institution study, only 8% of patients with NSCLC underwent surgical resection. The main reason for the low operative rate was the high proportion of patients who presented with advanced inoperable disease.³¹ Following surgical resection, the 5-year survival was 29% and the median survival was 27 months (Table III).³¹ Completeness of resection was the main determinant of survival outcomes. Complete resection had significantly better median survival than those in whom the tumour could not be totally removed (31 months vs 10 months). The overall five-year survival rate was 34% in the group with complete resection, whereas there was no patient with incomplete resection who survived to 5 years in this study.³¹

Chemotherapy and Radiotherapy

The majority of patients are diagnosed at an advanced or metastatic stage of disease in which case chemotherapy and/or concurrent administration of chemotherapy and radiation is the most beneficial form of treatment. Current chemotherapeutic drugs kill cancer cells mainly by inducing apoptosis. In a retrospective observational study on 814 cases of lung cancer between 2003 and 2009, treatment response (reduction in the size of the primary lesion) to chemotherapy

was observed after the 3rd cycle of treatment with gemcitabine plus cisplatin, and the 4th or 5th cycle for etoposide plus cisplatin. Reduction in number of metastasis and/or disappearance of cancer invasion was noticeable after the 5th cycle of treatment with gemcitabine plus cisplatin and the 6th cycle of treatment with etoposide plus cisplatin.³² In another study on 33 patients done by Leow, *et al*, at the same institution, patients who received gemcitabine-carboplatin combination chemotherapy over a 2.5 years period had a 27% overall response rate. The median survival rate among patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 1 was 11 months, as compared to 4 months in patients with ECOG performance status of 2, with the difference being statistically significant.³³ The results of this study also suggests that three cycles of cytotoxic chemotherapy may suffice as only 14% of all patients (2/14) undergoing the full course of six cycles showed further tumour regression. However, the number of patients in this study was very small and may not represent the actual response rate. Future studies involving larger numbers of patients should compare the efficacy of three-cycle and six-cycle regimens of carboplatin-gemcitabine combination chemotherapy.³³

In another study, data from two local institutions, Seremban General Hospital and Nilai Cancer Institute, were collected. The median survival of NSCLC patients who accepted cancer-specific therapy i.e. surgery, chemotherapy or radiotherapy, was significantly longer compared to those who opted out of cancer-specific treatment (8.6 months versus 2.2 months, $p<0.001$). However, despite the small significant survival benefit in accepting cancer-specific treatment, the overall prognosis for patients with NSCLC remains poor.³⁴ How, *et al* reported an overall median survival of 18 weeks in 149 patients with histologically confirmed lung cancer in their study. This study was conducted in a single referral hospital of the state of Pahang from 2007 to 2010. They also revealed that among NSCLC patients on treatment, 1- and 2-year survival rates were only 27% and 15% respectively. The median survival of patients who received treatment was 35 weeks as compared to 16 weeks for those who did not ($p<0.001$).³⁵

Hypercalcemia can occur in cancer patients with and without bone metastasis. Chemotherapy lowered serum calcium levels significantly in lung cancer patients who were initially hypercalcemic at diagnosis, in particular with chemotherapy regimen: Gemcitabine + Cisplatin (after the 3rd cycle of treatment) in lung cancer, probably by reducing parathyroid hormone-related protein ($p=0.003$).³²

Biologically Targeted Therapy

Recently, oncogenic driver mutations have been detected in NSCLC and tumours with mutations in oncogenes such as epidermal growth factor receptor (EGFR), ALK, ROS1 and others can be treated with appropriate oncogene-driven targeted therapy with improved outcomes. Tumours with EGFR deletions in exons 19 and 21 have improved response to treatment with EGFR-targeted tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib.

EGFR-TKIs have been approved as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. Studies have shown that when given alone, oral gefitinib showed significant durable anti-tumour activity in a significant proportion of Malaysian patients with locally advanced and metastatic primary adenocarcinoma of the lung.³⁶ The relatively high prevalence of epidermal growth factor receptor (EGFR) mutations predicting altered biology and more favourable response to EGFR tyrosine kinase inhibitors may explain the better survival rate of lung cancer patients in Asians compared to Caucasians.²⁹

A retrospective study done by the Liam and colleagues involving a total of 23 patients receiving gefitinib monotherapy reported disease control in 14 patients (61%); of these, 11 patients (48%) showed at least 30% reduction in tumour size of the primary and/or metastatic tumours (partial response), while 3 patients (13%) had stable disease (absence of either response or progressive disease for a minimum of 8 weeks). The response rate was significantly higher in those who had never smoked (10 of 15 or 67%) compared with that of smokers (1 of 8 or 13%) ($p=0.027$). The median time to symptom improvement was 1.5 weeks (range 0.5–6).³⁷ Adverse effects associated with gefitinib treatment were generally mild and consisted of grade 1 or 2 skin toxicity, which included dry skin, acne, pruritic rash, loss of finger nails and toe nails.³⁶ Another study done by the same authors several years later on advanced lung adenocarcinoma patients with unknown EGFR mutation status also similarly reported that the response rate to gefitinib was higher in women and never-smokers compared to men and ever-smokers.³⁷ They also reported that patients with good WHO performance status 1 or 2 had a response rate of 61%, whereas none of the patients with WHO performance status 3 or 4 responded to treatment given.³⁰

The phase III, randomized, open-label ENSURE study evaluated first-line erlotinib versus gemcitabine/cisplatin in patients from China, Malaysia and the Philippines with epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC). In this study, it was reported that the median progression-free survival was 11 months in the erlotinib group versus 5.5 months in the gemcitabine/cisplatin group, regardless of EGFR tumour mutation type (HR 0.34, 95% CI 0.22-0.51, $p<0.0001$), and objective response rate was 62.7% for erlotinib and 33.6% for gemcitabine/cisplatin.³⁹ Treatment-related serious adverse events occurred in 2.7% patients receiving first-line erlotinib compared to 10.6% of patients with cytotoxic chemotherapy (gemcitabine/cisplatin).³⁸

The use of EGFR-TKIs is associated with unique dermatologic side effects. Ong, *et al*, reported two cases of NSCLC developing atypical (papulo-pustular) eruptions shortly after initiation of EGFR-TKIs. Both patients received oral erlotinib and gefitinib following radiotherapy/chemotherapy. They developed acneiform over the face and upper trunk (after 10 days and 2 weeks commencement of erlotinib and gefitinib respectively). The cutaneous side effects of both patients resolved with oral doxycycline and topical benzoyl peroxide.³⁹

Lung carcinoma in pregnancy is rare especially in never smokers. Treatment of advanced lung cancer in pregnancy is challenging because one has to weigh the benefits and risks of treatment, both to the mother and the fetus. Compared to cytotoxic chemotherapy, EGFR tyrosine kinase inhibitors treatment is more effective, targeted and associated with fewer side effects. Lee, *et al*, reported a successful pregnancy in a patient diagnosed with stage IV lung adenocarcinoma with multiple lung secondaries and lymphangitis carcinomatosa, who showed both clinical and radiological responses to oral EGFR-tyrosine kinase inhibitor (Erlotinib and Gefitinib).⁴⁰

Traditional & Complementary Medicine

A study conducted by Lee, *et al*, showed the cytotoxic potential of the *Phyllanthus* plant in inhibiting A549 (lung carcinoma) and MCF-7 (breast carcinoma) cell growth by effectively reducing invasion, migration, and adhesion of the cells in a time- and dose-dependent manner ($p<0.05$). The extract of this plant had lower toxicity in normal cells with the cell viability percentage remaining above 50%. The authors concluded that the extract of various species of *Phyllanthus* was shown to be capable of inducing apoptosis in conjunction with its anti-metastatic action due to the presence of polyphenol compounds in the plant. However, the exact bioactive compounds in *Phyllanthus* exerting the anti-metastasis have not yet been identified.⁴¹

Distant metastases

The skeletal system is the most commonly affected organ in lung metastasis. A study done at University Malaya showed that 21% of primary lung cancer result in bone metastasis with male predominance observed ($n=21$, 65.6%). The survival of patients with metastatic disease is generally dependent on the type of primary tumour. Patients with primary lung cancer with bone metastases had the shortest mean survival time (16.0 ± 1.7 months) as compared to other primary cancer. This study also showed a marginally higher incidence of long bone metastasis than axial skeleton metastasis.⁴² The treatment of bone metastasis is usually palliative and aims to adequately control pain, and to anticipate or stabilize pathological fracture.⁴³

It is sometimes challenging to distinguish spinal tuberculosis from metastatic lung adenocarcinoma. Zamzuri, *et al* reported a rare case of metastatic adenocarcinoma of the lung to the spine with T7 vertebra body collapse which was thought to be spinal tuberculosis due to a positive Mantoux test and elevated erythrocyte sedimentation rate (ESR). However, the patient did not respond to anti-tuberculosis drugs. CT thorax subsequently revealed a peripherally located right lower lobe lesion which was an adenocarcinoma in histopathological examination.⁴⁴

Primary lung cancers also have tendencies to metastasize to the brain with an estimated incidence of around 20–40%. Patients with brain metastases from an underlying lung primary seem to fare less well in terms of overall survival compared with other primary tumour sites such as breast or colorectal cancer. A retrospective study by Tang, *et al* on 125 patients with confirmed non-small cell lung carcinoma and brain metastases reported the overall median survival of 3.4 months (95% CI: 1.7–5.1).⁴⁵ Median survival of patients with

multiple metastases receiving whole brain radiotherapy (WBRT) was 1.5 months, 1-3 metastases receiving WBRT was 3.6 months and 1-3 metastases receiving surgery or stereostatic radiosurgery/stereostatic radiotherapy was prolonged to 8.9 months (2.5 fold increase for those received on WBRT).⁴⁵ ECOG score, presence of seizure, treatment modalities (receiving either SRS/SRT±WBRT or WBRT alone) as well as receiving post-therapy systemic treatment were significant factors affecting prognosis on both univariate and multivariate analysis.⁴⁵

A case report revealed a rare complication of metastatic lung cancer leading to intussusception of the bowel. The patient presented with upper gastrointestinal bleeding suggestive of duodenal ulcer; subsequent CT thorax/abdomen showed a mass at the head of pancreas and lesion at the left lung. The histopathological examination of both lesions showed similar histology, findings were suggestive of small cell carcinoma of the lung with metastasis to the small bowel and pancreas, with an incidental finding of intussusception at the jejunum intra-operatively.⁴⁶

Catherine, *et al* published a case report describing two patients with metastatic lung cancer diagnosed during pregnancy. Both ladies were diagnosed to have lung carcinoma (squamous cell carcinoma and adenocarcinoma) at 31 and 35 weeks respectively. They managed to deliver healthy babies with adequate birth weight prematurely. However, due to the advanced stage of the disease, both of them did not survive. In both cases, palliative chemotherapy was declined because of the mothers' concern for their fetus. There is no published data on optimal chemotherapy and radiotherapy strategies for lung cancer patients who are pregnant.⁴⁷

PATIENT COMPLIANCE

Patients who fail to attend follow-up may after initial investigations result in delays in the appropriate treatment which affect outcomes. A prospective study was done by Ng, *et al* involving 95 patients aimed at determining the prevalence, patient characteristics and reasons for defaulting follow-up and treatment among patients with lung cancer. The prevalence of patients defaulting treatment and follow-up was 21% (20/95), two thirds of them were persistent defaulters (defined as defaulting two consecutive appointments), while the other one third were intermittent defaulters (defined as defaulting at least one follow-up or planned treatment at a given appointment date).⁵³ Most of the defaulters gave the reason of being "too ill" to come (39%) and logistic difficulties. There was no correlation between patient education, income, Eastern Cooperation Oncology Group (ECOG) performance status, stage of the disease, race or gender. However, education level of their children was found to be significantly associated with defaulter rate.⁵³ In another study, Hooi, *et al*, reported 16% of patients were lost to follow-up even with concerted efforts to locate them. Patients commonly requested for discharge from hospital once they are terminally ill and did not return for follow-up.³¹

SOCIAL IMPACT

Debilitating impact and traumatic effect of the diagnosis of cancer on the quality of life (QOL) of the afflicted individuals, their spouses and their families is inevitable. A cross-sectional study was performed recruiting 95 adolescent children from 50 families aged 13–18 years to parents who were suffering from colorectal, breast or lung cancer (the three most common cancers in Malaysia). Adolescents with parental cancer had significantly lower scores in emotional functioning ($p < 0.05$). Male adolescents had significantly higher quality of life overall and in physical functioning compared to female adolescents. Furthermore, monthly household incomes (household incomes of less vs more than RM 5,000) had significant differences in emotional QOL and school QOL.⁵⁴

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

This review of the research studies done in Malaysia contributes towards our overall knowledge, understanding and management of patients with lung cancer in the country. Lung cancer has been identified as an important cause of mortality and morbidity in the country;^{3,7} adequate resources must be allocated towards better primary prevention, earlier and more effective diagnosis, better treatment and palliation, and better support for patients and their families.

Smoking has been shown to be the main risk factor for lung cancer.^{5,6,48} Knowledge of this amongst the general public is good but there are still significant numbers of smokers in the country. Efforts are needed to discourage smoking amongst the population through both financial disincentives and restrictions on smoking in public places. Greater efforts must be made to increase the numbers and availability of smoking cessation clinics in the country, and every encouragement and incentive must be given to smokers to attend these clinics.

Public awareness of the symptoms, signs and nature of lung cancer was found to be poor.^{52,53} This has been identified as a cause of late presentation of the disease at an inoperable stage in many patients, and also a delay in diagnosis.⁶ Greater efforts must be made towards educating the public on the symptoms and signs of lung cancer and the need to seek early medical attention at a stage when the disease is still curable. In addition, protocols must be in place for general practitioners and physicians for early referral for imaging and other diagnostic procedures in patients with symptoms and signs suggestive of lung cancer.

Studies using bronchoscopy to obtain tissue diagnosis reported good diagnostic yields using bronchial washing (BW), bronchial brushing (BB), broncho-alveolar lavage (BAL), transbronchial biopsy (TBB) and endobronchial biopsy (EBB).^{21,22} Chest physicians must become familiar with these techniques with or without endobronchial ultrasound (EBUS) guidance and make this the standard of care.

Adenocarcinoma has been identified as the most common subtype of lung cancer in Malaysia (Table I).^{5,6} Studies have identified a large proportion of adenocarcinoma patients in

Malaysia with mutations in the epidermal growth factor receptors (EGFR), similar to other Asian countries but much higher rates compared to Western countries.^{28,29} These patients demonstrate increased responsiveness to treatment with EGFR-targeted tyrosine kinase inhibitors, with improved survival being reported.^{36,38} Testing for EGFR mutations in lung adenocarcinoma patients is therefore mandatory and all histopathology laboratories in the country receiving lung tumour biopsies and specimens must make this their routine practice and be adequately trained and equipped for this. In addition, EGFR-targeted tyrosine kinase inhibitor therapy must be readily available to chest physicians and oncologists.

Several small studies using chemo and radiotherapy in advanced lung cancer were reported.^{32,33} Insights were offered into the optimal choice, regime and duration of chemotherapy agents. However, these observations need to be confirmed in larger studies.

A study on the social impact of lung cancer on the patient's family and carers reminds us that support for the patient and family is needed beyond the medical treatment given.⁵⁴ This is too often forgotten and adequate training and provision of these services are needed in the country.

SECTION 3: FUTURE RESEARCH DIRECTION

An important observation of this review is that survival rates from lung cancer is poor mainly due to the advanced stage at which the disease is diagnosed in most patients precluding curative surgical resection (Tables I and III).^{4,5} Greater efforts must therefore be put towards earlier detection of the diseases. In addition to better education of the public on the symptoms and signs of lung cancer, screening of at risk individuals for lung cancer must be considered. The benefits of screening for lung cancer in at risk individuals, i.e. current or ex-smokers, has been demonstrated in a large randomized controlled trial in the United States, the National Lung Cancer Trial, where a 20% survival advantage was reported in the individuals screened by low dose CT scan.⁵⁵ However, it is unclear if such a screening programme is feasible in Malaysia where most CT scan departments are already working to capacity with existing clinical demand. Moreover, the incidence of false positive nodule detection in this country may be significantly higher given the higher incidence of tuberculosis in this country.^{16,17} A pilot feasibility study on lung cancer screening in this country is therefore necessary before we embark on a nationwide lung cancer screening programme. It is now possible to detect tumour DNA in circulating blood. Research is needed to determine if it may be possible to use this as a screening tool for lung cancer.

There is also an absence of comprehensive nationwide data on lung cancer diagnosis by disease stage, the treatments given, and the long term outcomes. The studies reported in this review in most cases covered individual centers. The National Cancer Registry has unfortunately not reported in recent years and also does not have comprehensive data on long term survival according to treatment modalities. There is a need for a comprehensive national database on lung cancer to better understand the true burden of disease, appropriateness of management and treatment of the condition, and the long term outcomes. To this end, the

recent launch of the National Thoracic and Cardiovascular Surgical Database (NCTSD) Registry is timely.

The high prevalence of exon 19 and 21 EGFR mutations in lung adenocarcinoma tumours amongst Malaysian patients is promising due to its improved responsiveness to EGFR inhibitors. However, acquired resistance to EGFR inhibitors develops after a period of treatment and research is needed to better understand and overcome this.

More recent developments in lung cancer therapy include the use of immunotherapy in advanced disease with the potential for improved survival. Genomic profiling and biomarker analysis is likely to identify tumours which would respond to immunotherapy. Studies on this are needed in the country as our population may differ from that in western countries where most of these research is currently being done.

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A Review of Acute Rheumatic Fever and Rheumatic Heart Disease Research in Malaysia

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ABSTRACT

A total of 39 titles related to rheumatic fever or rheumatic heart disease in Malaysia were found with online literature search dating back to their inceptions and through 2014. Additional publications from conference journals were included. Nine papers were selected based on clinical relevance and future research implications.

There were no population-based studies on the incidence or prevalence of ARF or RHD. In the 1980s, the incidence of admission due to ARF ranged from 2 to 21.1 per 100 000 paediatric admission per year. The burden of disease was significant in the adult population; 74.5% of patients with RHD were female, of which 77.1% were in the reproductive age group of 15-45 years old. Rheumatic mitral valve disease constituted almost half (46.7%) of all mitral valve repairs, ranging from 44.8 – 55.8 patients per year from 1997 – 2003. From 2010-2012, mitral valve interventions increased to 184 per year, of which 85.7% were mitral valve repair.

In children with ARF, 25.4% - 41.7% had past history of rheumatic fever or RHD. In patients with rheumatic mitral valve disease undergoing surgical or medical interventions, only 6% reported history of ARF, none had history of GABHS pharyngitis or antibiotic prophylaxis. Only 44.7% of patients with RHD on follow-up were on intramuscular benzathine penicillin prophylaxis.

Overall, there is scarcity of publications on ARF and RHD in Malaysia. Priority areas for research include determination of the incidence and prevalence of ARF and RHD, identification of high-risk populations, evaluation on the implementation and adherence of secondary preventive measures, identification of subclinical RHD especially amongst the high-risk population, and a surveillance system to monitor and evaluate preventive measures, disease progression and outcomes.

KEY WORDS:

Acute rheumatic fever, rheumatic heart disease, prevention, penicillin prophylaxis, Malaysia

INTRODUCTION

Acute Rheumatic Fever (ARF) is a postinfectious, immunologic response to untreated or inadequately treated Group A β -Hemolytic *Streptococcus* (GABHS) pharyngitis,

occurring in genetically susceptible individuals. Rheumatic heart disease (RHD) is the only chronic sequel to ARF, with lifelong consequences. As such, ARF and RHD are potentially preventable diseases with timely, adequate and appropriate antibiotic treatment of streptococcal pharyngitis.

Unfortunately, ARF and RHD remain the most important causes of cardiovascular morbidity and mortality in children and young adults living in developing countries,¹⁻³ and the poor and minority groups in developed countries.⁴⁻⁵ RHD is the most commonly acquired heart disease in these socially and economically disadvantaged population.¹⁻⁵ In 2005, it was estimated that 15.6 million people have rheumatic heart disease worldwide; and there were 282,000 new cases of rheumatic fever with 233,000 deaths attributable to rheumatic fever or rheumatic heart disease annually.¹ In Asia, it is estimated that up to 1% of all school children show signs of the disease.³ Studies from South-Central Asia produced prevalence estimates ranging from 0.68-1.3 per 1,000 school-aged children.³ A household survey in rural Pakistan found all-age prevalence of echocardiographically confirmed rheumatic heart disease of 5.7 per 1,000 population.⁶ A school-based survey conducted in Phnom-Penh, Cambodia found a prevalence rate of clinically detected RHD that was echocardiographically confirmed at 2.2 per 1,000 children.⁷ Studies using echocardiography to screen for RHD showed a marked increase in the prevalence,⁷⁻⁹ with a 10-fold increase to 21.5 cases per 1000 children in Cambodia,⁷ and an increase from 0.8/1,000 to 20.4/1,000 school children in India.⁹

The objectives of this review are to summarise the studies on ARF and RHD in Malaysia that have been published, to review the incidence, epidemiology, clinical features, and management of ARF or RHD, and to identify gaps in the management and research on ARF and RHD in Malaysia.

SECTION 1: REVIEW OF LITERATURE

LITERATURE SEARCH Rheumatic Heart Disease; Rheumatic Fever

PubMed search and other searches according to the search methodology of the National Clinical Research Centre¹⁰ with the Medical subheadings (MeSH) Rheumatic Fever OR Rheumatic Heart Disease AND Malaysia from 2000 – 2014 were conducted. Online literature search dating back to their

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inceptions and continuing through 2014 with the same MESH were also conducted. There were a total of 39 titles. Additional studies or publications from conference journals were hand searched and included in the review. The abstracts of the articles were reviewed and 9 papers were considered relevant. Case reports or case series were excluded. The abstracts or the fulltext of these 9 articles were reviewed.

There were 9 studies over a span of 25 years; 6 were retrospective studies,¹¹⁻¹⁶ and 3 prospective observational studies.¹⁷⁻¹⁹ All were hospital- or institution-based studies with 4 papers from the National Heart Institute Kuala Lumpur,¹⁶⁻¹⁹ 2 papers from University Hospital or Universiti Malaya Medical Centre Kuala Lumpur,¹²⁻¹³ and one each from Hospital Universiti Sains Malaysia Kota Baru,¹¹ Hospital Kuala Lumpur,¹⁴ and Queen Elizabeth Hospital II Sabah (Table 1).¹⁵ Six (66.7%) of these papers were recent and were published in 2013 and 2014.¹⁴⁻¹⁹

INCIDENCE AND PREVALENCE

There were no population-based studies on the incidence or prevalence of ARF or RHD in Malaysia.

In the paediatric population, there were 4 retrospective studies.¹¹⁻¹⁴ Two retrospective reviews of paediatric admission in the 1980s showed that the incidence of admission due to ARF ranged from 0.002% or 2 per 100 000 total paediatric admission per year,¹¹ to 21.2 per 100,000 paediatric admission per year.¹² Over a 30 year study period, the overall trend was a gradual decline in the number of new cases of ARF, with a peak of >50 cases in 1970-71 to the lowest of <10 cases per year in 1996-1997 in a single institution.¹³ In a more recent review, there were 20 patients diagnosed to have ARF and RHD over a period of 13 months (Table II).¹⁴

In the adult population, the prevalence of RHD contributed significantly to the workload in a tertiary heart centre, constituting almost half (46.7%) of all mitral valve repairs.¹⁸ From 1997 – 2003, the number of mitral valve repairs due to RHD ranged from 44.8 – 55.8 per year (Table II).^{17,18,19} In a more recent 3-year review from 2010-2012, the total number of patients with RHD who required mitral valve repair or PTMC increased to 184 per year, of which majority (85.7%) were mitral valve repairs.¹⁶ The age ranged from 3-75 years, with a mean age of 32±19 years¹⁸; 13% were children (Table II).¹⁶

CLINICAL FEATURES AND CARDIAC INVOLVEMENT

In the paediatric population, the peak age for ARF was in school-going children.¹¹⁻¹⁴ Fever and joint pain were the most common presenting features, present in 92.9% and 66.7% of patients respectively, followed by joint swelling in 57.1%.¹¹ Amongst the 37 patients with chorea, carditis remained the most common other feature of ARF (35%), followed by arthralgia (24%), fever (22%), subcutaneous nodules (11%), arthritis (5%), and erythema marginatum in 3% of patients.¹³

In the paediatric studies on ARF and RHD, there was an overall male preponderance with male to female ratio ranging from 1: 1.1 to 1.5:1.^{11,12,14} However, in the studies of both adult and children who required mitral valve repair due to RHD, there was female preponderance in the adult

population,¹⁵⁻¹⁸ with equal number of patients in the paediatric population (Table II).¹⁶ In an adult out-patient audit, 74.5% of the patients with RHD were female, of which 77.1% were in the reproductive age group of 15-45 years old.¹⁵

In both the paediatric and adult populations with ARF or RHD, mitral valve disease remained the most common valve complication.^{11,14-19} In the 1980s, amongst the children with ARF, 66.7% had carditis, of which 89.3% were mitral incompetence, 71.4% congestive heart failure, 28.6% mitral stenosis, and 17.9 % aortic incompetence.¹¹ These findings were similar in a more recent study on paediatric population where mitral regurgitation was present in 92% of patients (41.7% were severe mitral regurgitation) and aortic incompetence in 67% patients, where 16.7% had severe aortic regurgitation on echocardiographic examination.¹⁴ A total of 36.6% of these patients had severe congestive cardiac failure in New York Heart Association (NYHA) functional class III or IV; one patient required intubation and ventilation.¹⁴

Mitral regurgitation was the predominant valvular dysfunction in the paediatric patients with ARF or RHD,^{11,14} as well as in the adult patients with RHD.¹⁵ In the studies involving rheumatic mitral valve repair, most patients had mitral regurgitation; concomitant mitral regurgitation and stenosis occurred in 10.0 - 22.6% of all patients,^{17,18,19} whereas isolated mitral stenosis was present only in 1.9% of patients.¹⁸ (Table II). More than three quarters of all patients who required rheumatic mitral valve repair were in congestive cardiac failure in NYHA functional class II or more, and about a quarter had atrial fibrillation.^{17,18} No patients were reported to have stroke or endocarditis in these series of patients undergoing valve repair.

DIAGNOSIS AND MEDICAL MANAGEMENT

There were no studies on the clinical or echocardiographic criteria used for the diagnosis of ARF or RHD in Malaysia. In a study from year 2010-2012, most patients with rheumatic mitral valve disease who required surgical or medical intervention did not have a past history of ARF, only 6% reported history of ARF.¹⁶ In an earlier study from 1968-1975, a past history of rheumatic fever was elicited in less than half (43.8%) of pregnancies with rheumatic valvular lesions.²⁰

There were also no studies on the acute medical management of ARF, effectiveness of aspirin, steroids or other anti-inflammatory drugs and the outcome of the disease.

PROGRESSION OF DISEASE AND QUALITY OF LIFE

There were no studies on the progression of disease or the quality of life in patients with RHD.

PREGNACY AND RHD

Pregnancy increases the morbidity and mortality of both mother and baby in women with RHD and requires additional close monitoring by the obstetricians and the cardiologists. Amongst the female patients with RHD in the reproductive age group of 15-45 years old, 55.6% were given

Table 1: List of relevant articles on Acute Rheumatic Fever (ARF) and Rheumatic Heart Disease (RHD) from Malaysia

Author	Year Published	Title	Type of Study	Population	Time Frame	Sample Size
Studies on epidemiology of Acute Rheumatic Fever / Rheumatic Heart Disease						
Gururaj AK <i>et al</i> ¹¹	1990	A Clinical, Laboratory and Echocardiographic Profile of Children with Acute Rheumatic Fever	Retrospective clinical study	Paediatric patients admitted to Hospital Universiti Sains Malaysia, who were diagnosed with ARF	Apr 1985-Mar 1989	42
Omar A ¹²	1995	Pattern of Acute Rheumatic Fever in a Local Teaching Hospital	Retrospective clinical study	Patients admitted to Department of Paediatrics, University Hospital who were diagnosed with ARF	Jan 1981 – Dec 1990	134
Chew NK <i>et al</i> ¹³	2002	A clinical study of Sydenham's chorea at University Malaya Medical Centre (UMMMC)	Retrospective clinical study	Patients admitted to UMIMC presenting with acute rheumatic fever	1967-1997	313
Hung LC <i>et al</i> ¹⁴	2013	Rheumatic heart disease in a tertiary hospital in Malaysia	Retrospective clinical study	Patients diagnosed with ARF or RHD in Paediatric Cardiology Unit, Hospital Kuala Lumpur	Jul 2011 – Jul 2012	20
Studies on Rheumatic Heart Disease, Consequences and Treatment						
Liew HB ¹⁵	2014	Audit of rheumatic heart disease outpatient service	Retrospective clinical study	RHD outpatients at Queen Elizabeth Hospital, Sabah	May – Jun 2013	47
Levin BR <i>et al</i> ¹⁶	2014	Epidemiology, clinical profile and cardiac remodeling of severe rheumatic heart disease in Malaysia	Retrospective clinical study	Patients with clinically severe RHD who underwent either PTMC or surgery, IJN	2010 - 2012	552
Dillon J <i>et al</i> ¹⁷	2013	Leaflet extension in rheumatic mitral valve reconstruction	Prospective clinical Study	Patients with RHD who underwent leaflet extension, National Heart Institute (IJN)	Jan 2003 – Dec 2010	62
Mohd Azhari Yakub <i>et al</i> ¹⁸	2013	Contemporary long-term results of mitral valve repair in rheumatic heart disease	Prospective clinical study	Patients who underwent MV repair for rheumatic mitral disease at IJN	Jan 1997 – Dec 2010	627
Dillon J, <i>et al</i> ¹⁹	2014	Comparative long-term results of mitral valve repair in adults with chronic rheumatic disease and degenerative disease	Prospective clinical Study	Patients admitted to IJN for rheumatic and degenerative mitral valve repair	1997 - 2010	401

Table II: Reported prevalence, demographics and cardiac involvement of ARF and RHD from 1985 through 2013 in Malaysia

Population	Time Frame	Sample Size	Incidence/prevalence	Demographics	Cardiac Involvement
Gururaj AK <i>et al</i> ¹¹	Apr 1985-Mar 1989	42	2 /100 000 paediatric admission per year	Range: 5.75 years to 11.9 years. All children were Malays. Male to female ratio: 1: 1.1	MI: 89.3%, MS: 28.6% AI: 17.9 % CCF: 71.4% Past history ARF/RHD: 26.2% There were 34 episodes of recurrent attacks in 20 patients.
Omar A ¹²	Jan 1981 – Dec 1990	134	21.2 /100 000 paediatric admission per year (15.8 first attack of ARF, 5.4 recurrent ARF)	Peak: 6 – 11 years, >63% Youngest: 4 years old Male to female ratio: 1.4: 1	35% had carditis during the first presentation of chorea.
Chew NK <i>et al</i> ¹³	1967-1997	Total: 313 Chorea: 37 (12%)	1970-1971: >50 cases/year 1996-1997: <10 cases/year	Onset of chorea: Mean age: 11.5 years Range: 2-12 years	MI: 92% AI: 67% 5/12 (41.7%) of ARF were recurrent ARF.
Hung LC <i>et al</i> ¹⁴	Jul 2011 – Jul 2012	20	20 patients over 13 months	Peak: 5-9 years old, 58.3% Male to female ratio: 1.5:1	MI: 74.5%
Liew HB ¹⁵	May – Jun 2013	47	47 patients over 2 months	Mean age 37 years old Female: 74.5%	Adult: none had reported history of GABHS pharyngitis or antibiotic prophylaxis.
Levin BR <i>et al</i> ¹⁶	2010 - 2012	Total: 552 Surgery: 85.7%	Overall: 184 patients per year Surgery: 157.7 per year.	Child:72. Surgery:70 Adult: female 66% Child: female 50%	MI: 77.4% MI + MS: 22.6% AF: 22.6% CCF: 77.4%
Dillon J <i>et al</i> ¹⁷	Jan 2003 – Dec 2010	Total 446 LE: 62	Total: 55.8 patients per year LE: 7.8 patients per year	Mean age 20.2±11.7 years, range 3-60 years. Female: 75.8%, male: 24.2%	MI: 85.6% MI + MS: 12.4% Isolated MS: 1.9% AF: 22.6% CCF: 76.8%
Mohd Azhari Yakub <i>et al</i> ¹⁸	Jan 1997 – Dec 2010	627	44.8 patients per year	Mean age: 32±19 years Range 3-75 years, median 28 years. Female: 54%, male 46%	R: 90% MI, 10% MI + MS R: 90% MI, 10% MI + MS
Dillon J, <i>et al</i> ¹⁹	1997 - 2010	Total: 401 R: 268 D: 157	R: 19.1 patients per year D: 11.2 patients per year	R: mean 53.9±8.4, median 53 yrs D: mean 55.8±7.4, median 55 yrs	

AF: Atrial Fibrillation. AI: Aortic Incompetence. CCF: Congestive Cardiac Failure, NYHA II or more. D: Degenerative. LE: Leaflet Extension. MI: Mitral Incompetence. MS: Mitral Stenosis. R: Rheumatic.

Table III: Freedom from reoperation and valve failure, comparing mitral valve repair performed for RHD versus degenerative disease

Author / Study Year	Condition	In-hospital or early mortality (%)	Freedom from reoperation at 5 years (%)	Freedom from reoperation at 10 years (%)	Freedom from valve failure at 5 years (%)	Freedom from valve failure at 10 years (%)
Mitral Valve Repair						
Mohd Azhari <i>et al</i> ¹⁸ 1997 – 2010	RHD	Overall 2.4	91.8 ± 4.8	87.3 ± 3.9	85.6 ± 2.3	72.8 ± 4.6
	Degenerative valve disease		92.0 ± 1.7	91.8 ± 4.8	88.7 ± 5.1	82.4 ± 7.7
Dillon J <i>et al</i> ¹⁹ 1997 - 2010	RHD	4.8	97.9	96.5	95.3	89.9
	Degenerative valve disease	1.9	94.3	94.3	92.0	89.4
Leaflet extension						
Dillon J, <i>et al</i> ¹⁷ 2003-2010	RHD	-	96.8	-	91.6	-

education on family planning, but only 25.9% had formal referral to family planning services.¹⁵

In a hospital-based study from the year 1968 – 1975 in University Hospital Kuala Lumpur, out of a total of 20,903 deliveries, 151 patients had cardiac diseases, of which 137 (0.66%) were associated with RHD. Mitral valve disease constituted 74.8% of the cardiac lesions, followed by 18.5% of both mitral and aortic valve involvement, and 5.9% isolated aortic valve disease. Less than 50% of these pregnancies ended up as normal vaginal deliveries compared to 78.1% in the hospital population over the same period. There was one maternal death amongst the 151 deliveries in mothers with cardiac lesions, giving a maternal mortality rate of 6.6 per 1000 deliveries.²⁰

RECURRENT ATTACKS OF RHEUMATIC FEVER AND PREVENTION

In the paediatric series, 25.4% - 41.7% of patients with ARF had past history of rheumatic fever or RHD.^{11, 12, 14} There were no data on secondary antibiotic prophylaxis in these studies.^{11,12,14}

Secondary prophylaxis is an important aspect of RHD management. In a recent outpatient audit of adults with RHD in Queen Elizabeth Hospital II, Sabah, it was found that only 44.7% were on intramuscular benzathine penicillin prophylaxis; 38.3% were not on any prophylaxis and 17.0% were on oral penicillin. Amongst those who were not on prophylaxis, 29.8% were patients aged more than 40 years old, whom were considered less vulnerable to recurrent carditis.¹⁵

In the study of 552 patients who required mitral valve repair or percutaneous transvenous mitral commissurotomy (PTMC) from 2010-2012, none had reported history of GABHS pharyngitis or antibiotic prophylaxis.¹⁶

There were no studies on primary or primordial prevention of ARF.

CARDIAC SURGERY AND OUTCOME

There were 3 studies from a single institution focusing on the surgical techniques and procedures and the outcomes of surgical repair of the rheumatic mitral valve.^{17,18,19} One study

from the same institution focused on the cardiac re-modelling after mitral valve repair or PTMC.¹⁶

Repair of rheumatic mitral valvular disease contributed 46.7% of the total number of mitral valve repairs in a major cardiac institution in the country.¹⁸ The number of mitral valve repairs increased over the last 2 decades from 44.8 per year from 1997-2010, to 157.7 per year from 2010 to 2012 (Table II).¹⁶

Early mortality from rheumatic mitral valve repair ranged from none in the leaflet extension group¹⁷ to 4.8%,¹⁸ whereas the in-hospital mortality rate for mitral valve repair in adults with degenerative valve disease was 1.9%.¹⁹

In all studies, the freedom from reoperation 5 years after the initial mitral valve repair was more than 90%, while the freedom from valve failure at 5 years was lower, ranging between 86 – 95%.^{17,18,19} At 10 years post-surgery, freedom from valve failure for the RHD group dropped further to 73% in one study,¹⁸ worse than the degenerative mitral valve disease at 82 - 89%.^{18, 19} (Table III)

LIMITATIONS OF REVIEW

Of the 9 papers, 4 were abstracts presented at conferences.^{14,15,16,19} Of the 5 full articles, 3 were retrospective review of medical records^{11,12,13} and 2 were based on prospective observational registry data^{17,18} that could have inherent potential biases.

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Overall, there is lack of research and good data on ARF and RHD in Malaysia.

INCIDENCE, PREVALENCE AND BURDEN OF DISEASE

Malaysia has made significant progress and development over the last few decades. As such, it is generally perceived that the incidence or prevalence of RHD is on the decline. Though there were no population-based studies on the incidence or prevalence of ARF or RHD in Malaysia, there was an overall decrease in incidence of ARF between 1967 to 1997 in a retrospective institutional-based review of clinical records.¹³

However, recent publications show that the prevalence of ARF and RHD is still significant.¹⁴⁻¹⁹ Rheumatic mitral valve repair constituted almost half (46.7%) of the workload of mitral valve repair in institutional prospective studies.¹⁸ Over the last two decades, the number of rheumatic mitral valve repairs has increased from 44.8 per year from 1997-2010, to 157.7 per year from 2010 to 2012 (Table II).¹⁶ These figures might not reflect the trend of disease as other factors such as increased awareness amongst healthcare professionals regarding the disease, lower threshold or criteria for surgical repair, and geographical or institutional bias in the pattern of referral for cardiac intervention may play a role.

From 1997 - 2010, the ages of the 627 patients who underwent rheumatic mitral valve repair ranged from children as young as 3 years old to the elderly of 75 years old,¹⁸ suggesting that ARF and RHD affected almost all age groups, except infants. Cardiac surgery indicates severe disease or eventual sequel of RHD, and the number of patients undergoing cardiac surgery merely represented the tip of the iceberg.²¹ In this study,¹⁸ the criteria for diagnosis of RHD were not discussed.

In addition to lack of data on the incidence and prevalence of RHD in the general population, Malaysia also lacks data on the incidence or prevalence of RHD amongst the indigenous population in the country. Studies in Australasia and Canada reported higher incidence of ARF and RHD in members of the minority or indigenous groups.^{4,5}

DIAGNOSIS OF ARF AND SUBCLINICAL RHD

There is no specific clinical feature or definite laboratory test to diagnose ARF. Since 1944, a constellation of clinical features and laboratory tests included in the Jones criteria have been used for guidance in the diagnosis of ARF. The American Heart Association (AHA) made several modifications and revisions to the Jones criteria over the last few decades.^{22,23} These revised or modified Jones criteria were used in the studies on ARF.^{11,12,13} With the development of echocardiography, some national and regional guidelines have included the use of echocardiography and Doppler studies in the guidelines for the diagnosis of ARF.^{24,25} In 2015, the AHA has included Doppler echocardiography in the revised Jones criteria for the diagnosis of ARF.²⁶

In a study from 1968-1975, a past history of rheumatic fever was elicited in less than half (43.8%) of pregnancies with rheumatic valvular lesions.²⁰ A more recent study from 2010-2012 on adult patients who required rheumatic valvular repair or PTMV revealed that none had reported history of GABHS pharyngitis or on antibiotic prophylaxis and only 6% reported a history of ARF.¹⁶ These might be due to lack of awareness regarding the importance of GABHS pharyngitis, ARF and its recurrence among healthcare providers and the community, poor patient education, or a high incidence of subclinical ARF or RHD.

Screening and early detection of subclinical RHD could reduce the prevalence and severity of RHD by effective implementation of secondary antibiotic prophylaxis and surveillance. Numerous studies have shown that transthoracic echocardiography examination could detect

mild or subclinical rheumatic valvular disease which could not be diagnosed by clinical examination, and revealed a much higher RHD burden than previously thought.^{7,8,9,27,28,29} In 2012, the World Heart Federation developed and published an evidence-based guideline on the echocardiographic criteria for the diagnosis of RHD.³⁰ To minimise the utilisation of resources in these resource-poor developing countries, different approaches were also studied to determine the accuracy of echocardiographic screening.^{31,32} Handheld echocardiographic screening for RHD by non-experts had shown reasonable sensitivity (74.4%) and specificity (78.8%) for both borderline and definite RHD, and improved to 90.9% for definite RHD.³²

PROGRESSION OF DISEASE, QUALITY OF LIFE AND OUTCOME

Good health and well-being are the goal of medicine. However, medical and surgical treatment of severe rheumatic valvular disease are at best palliative, and these are neither accessible nor affordable to the majority of the affected patients who are poor and young. The mean age for mitral valve repair was 20-30 years old.^{17,18} This is the young and productive age-group when an individual is at their prime. Unfortunately, RHD has compromised their quality of life from a young age.

In addition, amongst the adult patients who required rheumatic mitral valve repair or intervention, there was female preponderance.¹⁵⁻¹⁸ In an adult out-patient audit, 74.5% of the patients with RHD were female, of which 77.1% were in the reproductive age group of 15-45 years old.¹⁵ These patients require more medical care during their antenatal, intrapartum and postnatal period; and have higher rates of morbidity and mortality for both the mother and the baby. There were no recent publications on the outcome of pregnancy in these patients.

ARF recurrences cause progressive valvular damage and can lead to complications such as congestive cardiac failure, atrial fibrillation, stroke or infective endocarditis. About three quarter of patients undergoing rheumatic mitral valve surgery had congestive cardiac failure and a quarter had atrial fibrillation.^{17,18}

RECURRENT ATTACK OF RHEUMATIC FEVER AND PREVENTION

Secondary prevention of recurrent ARF with regular intramuscular benzathine penicillin injection to prevent recurrent streptococcal pharyngitis and progressive valvular damage, is an important and proven cost-effective measure to reduce the burden of ARF and RHD on both the population and the healthcare system.^{33,34}

In Malaysia, the recurrence rate of ARF was high, ranging from 26.2% to 41.7% amongst children with ARF or RHD.^{11,12,14} In an outpatient audit, less than half the adult patients received intramuscular benzathine penicillin.¹⁵ In the patients who required mitral valve repair or PTMC, none had reported history of GABHS pharyngitis or antibiotic prophylaxis.¹⁶

As such, ensuring appropriate implementation of secondary antibiotic prophylaxis, and a surveillance system to monitor adherence to treatment are important measures to prevent recurrent streptococcal pharyngitis and progressive valvular damage, in order to reduce the burden of ARF and RHD in the country.

Primary prevention, which includes accurate diagnosis, and adequate and timely treatment of the initial acute streptococcal infection with an appropriate antibiotic, is the other important preventive measure. Ultimately, primordial prevention with eradication of poverty and provision of proper housing should be the goals of the authority or the government.

CARDIAC SURGERY

As the disease progresses, valve repair or replacement often becomes necessary. Patients who do not have access to such expensive surgery may have poor quality of life and die prematurely from RHD or its complications. ARF and RHD are neglected diseases of the poor and the marginalised in their youth or young adulthood, who usually do not have access to such expensive surgery. Even with valve surgery, the longterm outcome maybe worse than degenerative valves.¹⁸ As such, prevention of ARF and RHD is imperative.

SECTION 3: FUTURE RESEARCH DIRECTIONS

Overall, there is scarcity of publications on ARF and RHD in Malaysia. Priority areas for research include determination of the incidence and prevalence of ARF and RHD in Malaysia, identification of high-risk populations, evaluation of the implementation of secondary preventive measures and adherence to intramuscular benzathine penicillin injection, identification of subclinical RHD especially amongst the high-risk population, and a surveillance system to monitor and evaluate preventive measures, as well as disease progression and outcome.

In Malaysia, most patients who required cardiac surgical intervention had subclinical RHD. Research in the detection of subclinical RHD in high-risk populations with transthoracic echocardiographic examination, and proper implementation of secondary antibiotic prophylaxis with intramuscular penicillin injection in these high-risk population should be another area to explore. Progression of disease, quality of life, morbidity and premature deaths can then be determined.

Evaluation of the human, social and economic costs, cost-effectiveness of early detection of subclinical RHD, and implementation of preventive measures and their effectiveness, can help in the future development of policies, planning of RHD programmes, resource allocation for primary and primordial prevention, as well as tertiary cardiac care programmes and surveillance programmes.

ARF and RHD contributed significantly to the surgical burden of mitral valve repair or replacement in the country. Since the reduction in disease progression or severity has a long lag time, reduction in the burden of surgical repair of rheumatic

mitral valve may be seen only at a much later date. In addition to the provision of data on the surgical repair of rheumatic heart valves, the National Cardiothoracic Registry that was launched in 2015 can be a source of data for research on the epidemiology, demographic and quality of life in Malaysia.

Public health priorities may include research on the evaluation of the effectiveness of rapid diagnosis of streptococcal pharyngitis, primary prevention through public education to increase the awareness of the people on the importance of timely and adequate treatment of acute streptococcal pharyngitis, and effort to empower children and the community to seek treatment with appropriate antibiotics.

In May 2012, the United Nations and the World Health Assembly agreed to adopt a global target to reduce premature non-communicable diseases (NCDs) mortality by 25% by 2025.³⁵ RHD is a disease where this may be achievable because there are relatively inexpensive, proven, and effective control strategies that can lead to decrease in deaths, especially in young people.³⁶

The World Heart Federation Working Group on RF and RHD was established in 2011 to achieve its goals in the control of RF and RHD.³⁷ Unlike other NCDs, RHD is preventable. As such, research on ARF and RHD, and the incorporation of RHD into the national NCD prevention programmes should be top priorities. With these concerted efforts, Malaysia may be able to achieve the United Nations and the World Health Assembly's target of reducing premature NCD mortality by 25% by 2025, especially amongst poor women and children who are most affected with RHD.

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A Review of Research on Child Abuse in Malaysia

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ABSTRACT

The aim of this review was to summarise published literature on child abuse and neglect and its consequences in Malaysia, to discuss the implications of the research findings and to identify gaps in the local literature on child abuse and neglect. Medical and social literature in the English language published between the year 2000 to 2015 were searched for, resulting in forty four papers to be reviewed inclusive of a few key papers in the earlier years to provide some background information. The literature shows that child abuse and neglect is an important impact factor on mental health outcomes, involvement in substance abuse and delinquency due to the slant of the research interest from social studies. At least 70% of perpetrators are known to the affected children according to school-based prevalence studies. Safety programs and rehabilitation outcome studies involve small cohort groups. Studies on childhood mortality from child abuse or neglect are very limited. Overall, there are a few comprehensive studies involving school children but overall available studies are too patchy in to advocate for resource allocation, change in statutory procedures or training requirements. More extensive studies looking at the complex interaction of social environment, parenting skills, societal attitudes and responses, resilience factors and child safety nets and statutory response and their impact on different types of abuse or neglect are required.

INTRODUCTION

Child abuse and related experiences (or known as child maltreatment) have recently been recognised by the World Health Organisation as having broad implications for human development and the prevention of public health problems.¹ It is an important cause of childhood morbidity in terms of its impact on physical health and disability, emotional health, and healthy child development. In addition, the long term impact is not limited to the individual child victim but also on society from its effects on family, psychosocial consequences, juvenile delinquency, substance abuse and crime.² The economic burden of child maltreatment is also substantial, with an estimated economic value of DALYs lost ranging from 1.24% to 3.46% of GDP across sub-regions in the Asia and Pacific region defined by the World Health Organization. When updated to 2012 dollars, the estimated economic burden totaled US \$194 billion. This indicates the importance of preventing and responding to child maltreatment at the country and regional level.³

Malaysia ratified the Convention of the Rights of the Child (CRC) since 1995, which recognises the universally accepted right of the child as contained within this convention and the United Nations Convention on the Elimination of All Forms of Discrimination against Women (CEDAW).⁴ The Ministry of Women, Family and Community Development has been tasked by the government to lead and coordinate issues regarding women, family and children.

In the past, the public, as well as related professionals, often perceived instances of child abuse to be isolated cases rather than part of a widespread phenomenon. As a result, child maltreatment did not receive widespread attention until late-80s when a few high-profile abuse incidents of children were highlighted in the media.⁵ These acted as the catalyst in prompting the government to introduce the Child Protection Act in 1991. In addition, the one-stop crisis centres were set up in government hospitals around Malaysia beginning mid 1998 providing services for victims of domestic violence, sexual assault and child abuse.⁴ The government initiated a hotline, which was launched in April 1998.⁵ Since the introduction of *Child Protection Act 1991*, doctors are subject to mandatory reporting of any suspected child abuse case to the relevant authorities. The *Child Protection Act 1991* has been superseded by the *Child Act 2001* in an attempt to deal more effectively with issues relating to children.

Under the *Child Act 2001*, "child abuse" is defined as when the child has been or is at substantial risk of being physically or emotionally injured or sexually abused or neglected in terms of adequate care, food, shelter, clothing, medical attention, supervision and safety, or abandonment or others such as being on the street or used for begging by the parents or persons in charge of the child at any one time¹. From the health perspective, child abuse constitutes all forms of physical abuse and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm, to the child's *health, survival, development or dignity* in the context of a relationship of responsibility, trust or power⁶.

There is mandatory reporting for all cases of suspected child abuse by doctors, family members and childminders under the *Child Act 2001*¹. Data on reported child abuse are compiled annually mainly by the Department of Social Welfare, the Royal Malaysian police and various hospitals. Efforts by various agencies to setup a coordinated system of data collection between agencies are still ongoing. This is to ensure documentation of reported cases besides identifying

¹ Laws of Malaysia, Child Act 2001, Section 17 (i)-(k)

Table I: Total cases of child abuse and neglect reported to Department of Social Welfare, Malaysia from 2000-2010 according to type of abuse

Year	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Abandoned	n.a	n.a	n.a	71	70	121	98	26	68	53	63	58	62	115
Neglect	252	252	250	183	303	357	389	563	601	682	761	952	981	1250
Physical	476	489	413	362	287	354	410	445	431	495	586	863	895	846
Sexual *	219	270	291	258	251	324	430	529	566	679	754	733	728	937
Incest	n.a	n.a	n.a	n.a	n.a	n.a	n.a	30	57	49	21	72	n.a.	n.a.
Emotional	55	36	17	24	56	32	32	63	77	50	45	90	98	71
Others	147	104	136	36	69	54	31	0	0	0	49	12	25	38
Total	1149	1161	1107	934	1036	1242	1390	1656	1800	1999	2279	2780	2789	3257

Source: Department of Social Welfare, 2012

Note: *Excludes incest if figures for incest available

overlapping reports or cases which may have been recorded only by one of the agencies and not the others. The Ministry of Health has also developed a guideline for hospital management on child abuse and neglect by Suspected Child Abuse and Neglect (SCAN) teams in hospitals⁷ as well as the One Stop Crisis Centers (OSCC) in emergency departments.⁸ Table I shows the annual data from reports to the Department of Social Welfare according to the various types of child abuse, showing increasing numbers of reports.

AIM AND METHODS

The aim of this review was to summarise published literature on child abuse and neglect and its consequences in Malaysia, to discuss the implications of the research findings and to identify gaps in the local literature on child abuse and neglect.

The following search strategies were used to retrieve relevant articles for this review. Literature in English language was systematically searched using the following databases; PubMed, OVID and SciDirect. Searches were carried out for studies published from 2000 to 2015. Reference lists of all selected articles were reviewed to identify other relevant papers. The full-text containing sufficient details to determine the eligibility of all potentially relevant studies was reviewed. Key papers before the year 2000 were also included to provide some background to the development of child abuse recognition and research in Malaysia.

The databases were searched using controlled terms (e.g. Medical Subject Headings in Medline) and free text words. The following search was used most frequently: "Child abuse and neglect, child maltreatment, child protection or childhood trauma" OR "physical" or "sexual" or "emotional" or "psychological" or "neglect" or "incest" or "rape" or "corporal punishment" or "victimization" or "violence" or "injury" or "bully" AND "Malaysia" or "Asia". The search through database resulted in 1468 titles. Upon screening, there were potentially 76 useful titles for the review. Two reviewers (ICGS and CWY) screened all the titles to find eligible studies. Forty-four publications broadly related to child abuse and neglect in Malaysia were found to be relevant.

SECTION 1: REVIEW OF LITERATURE INCIDENCE AND PREVALENCE OF CHILD ABUSE AND NEGLECT IN MALAYSIA

There are relatively few studies on child abuse prevalence in Malaysia. The earliest prevalence study on childhood sexual abuse was published in 1996.⁹ Data on CAN prior to this publication were based on notification of cases. Singh and colleagues (1996) conducted a self-administered survey among 616 student nurses and trainee medical assistants at a nursing school and a medical assistant training school. About 6.8% of the students reported being sexually abused (questions included exhibitionism, molestation, sodomy and vaginal rape) during childhood of which 2.1% were males and 8.3% females. Less than 1% reported having experienced sexual penetration. Sexual abuse was reported to have begun under 10 years of age in 38.1% of the cases. About two-thirds of them were repeatedly abused and one third of them experienced abuse from more than one perpetrator. About 71.4% of the abusers were persons known to the respondent. A marked difference in prevalence between ethnic groups were found where more Chinese reported being sexual abuse victims than Malay and Indian. However, it cannot be determined if this was a result of under-representation from Chinese participants, or under-reporting of other ethnic groups due to local sociocultural limitations in disclosing abuse. Kamaruddin (2000) in another publication had cited several barriers to reporting of sexual abuse including societal discrimination against people who have been sexually abused, cultural taboos in relation to 'losing face' and lack of specialized 'one stop' centres at the time for the sexually abused.¹⁰ Though the target sample of Singh et al's study may not be entirely reflective of the population due to underrepresentation of Chinese and non-random sampling limiting the generalizability of the results, this study marked the beginning of systematic examination on the magnitude of the CAN at the population level in Malaysia.

Subsequent community based studies had measured CAN among school-going students,^{11,12} trainees in national service camps¹³ and incarcerated youths.¹⁴ Choo and colleagues (2011) conducted a cross-sectional survey among 1,870 students aged 16 years attending 20 randomly selected urban and rural secondary schools in the year 2005 in Selangor.¹¹ In this survey, a comprehensive set of questions addressed four domains of victimisation including sexual, physical, emotional and neglect, were administered. Emotional and physical maltreatment were the most common forms of child maltreatment reported. Depending on the type of abusive

behaviours, lifetime prevalence reported ranged from 13.5% - 72.3% for emotional abuse and 1.8% to 63.3% for physical abuse. A significant proportion of adolescents (22%) were exposed to multiple types of abuse. Compared with females, males reported more physical, emotional and sexual victimisations. Interestingly, there was no difference between males and females in reporting the most severe form of sexual abuse, penetrative or intercourse (3.0%), which differs from western literature suggesting that females are of higher risk of CSA. One such study showed a lifetime experience of sexual abuse of 26% in 17 year old females vs. 5.1% prevalence in males.¹⁵ The relative gender equivalence in unwanted sexual experiences in our study appeared to be consistent with other studies reported in some parts of Asian countries.¹⁶⁻¹⁸

In another cross-sectional study of 6786 adolescents aged 17-18 years in nine national youth camps between year 2008 and 2009,¹³ the rate of lifetime sexual abuse involving physical contact was 21.3% comparatively higher than in Choo and colleagues' study.¹¹ Although this study cannot be extrapolated to national prevalence as there is over-representation of Bumiputera Sabah (18.4%) and Bumiputera Sarawak (7.5%) indigenous groups in the study population, the findings suggest a possibility of a higher prevalence of sexual abuse among Sabah and Sarawak indigenous groups that should be further explored.

Ahmad and Mazlan (2014) compared the prevalence of childhood trauma in young adults who were and were not in detention. In the non-detained group of 674 participants, less than 10% of boys and less than 5% of girls had experienced moderate to extreme abuse. In comparison, about 30% of the detained boys had experienced moderate to extreme physical neglect and 15% experienced emotional neglect in the past. Thirty nine percent of incarcerated girls had experienced moderate to extreme physical abuse and sexual abuse.¹⁴

More recently, a separate cross sectional study involving 3509 ten to 12-year old children selected using a random sampling of public primary schools in Selangor estimated the prevalence of parental physical and emotional maltreatment, parental neglect and teacher-inflicted physical maltreatment.¹² Results were adjusting for weighted samples to extend results to a population level. Three quarters of 10-12 year-old children reported at least one form of maltreatment, with parental physical maltreatment being most common. The prevalence of parental physical maltreatment (53%), approaches the upper end of the range of physical abuse recorded in surveys from other countries reported in East Asia and the Pacific region (from as low as 0.4% for very severe abuse to as high as 66.3% for moderate physical abuse).¹⁹ Teacher-inflicted physical maltreatment was reported by 29% whilst approximately 1 in 5 children reported being emotionally maltreated. Males had higher odds of all types of maltreatment except for emotional maltreatment.¹²

The prevalence figures reported in these studies support the observation that child abuse and neglect is not an uncommon phenomenon in Malaysia, in particular physical maltreatment, neglect and emotional maltreatment. More

importantly, child sexual abuse is far more prevalent than actually reported to the authorities.

RISK FACTORS OF CHILD ABUSE AND NEGLECT

Early hospital-based studies indicate that low socioeconomic status (social classes IV and V), family disharmony or disruption, and divorced or separated parents, personality disorders and parental substance abuse were associated with child physical abuse.²⁰ Another study among cases confirmed in Kuala Lumpur General Hospital showed that sociodemographic factors surrounding child sexual abuse included being female, absence of another adult at home, unemployment, and history of drug abuse among the perpetrators.²¹ Ahmad *et al* (2010) in their qualitative interviews with incest survivors found that hardship and financial difficulties faced by the families forced the parents especially the mothers to work long duration of hours. This situation allowed children to be unsupervised by their mothers, allowing fathers to take advantage of their time alone with their children to sexually abuse them.²² While these studies provide information about probable determinants of child maltreatment in Malaysia, they are limited to clinical cases, which may reflect the more severe end of the spectrum and provide less indication of the risk factors associated with unreported cases.

Community based studies investigating risk factors of child maltreatment remains lacking. Among those reported possible risk factors of child maltreatment, domestic violence has been consistently linked with child maltreatment and this pattern is observed in two school-based studies.^{11, 12} Poor quality of child-parent relationship also shown to be a significant factor. Low regard of child relationship with parents might reflect poor parenting style and poor paternal attachment or impaired parental bonding, which has an indirect causal relationship with maltreatment. Interestingly, family structure (parental divorce, presence of step-parent or single parent, or household size), parental drug use, and geographical location (urban/rural) were not influential in both studies probably due to low incidence of single parents and drug abuse reported in this study.^{11, 12}

The existing research examining the effect of the larger environment such as neighbourhood and community context to CAN is less explored in Malaysia although several studies in developed countries have documented a possible relationship, using a number of measures of neighbourhood such as demographic composition, economic disadvantage or poverty, residential mobility, proportions of neighbourhoods on public assistance, level of crime, density of alcohol outlets.²³⁻²⁵ Although it is unclear why neighbourhood characteristics are correlated with child maltreatment, other studies suggested it may be explained by differences in availability of social resources, social network or social supports, social disorganisation and lack of social coherence,^{26, 27} or collective efficacy.²⁵ Choo and colleagues (2011) utilised subjective measurement asking respondents' perception of their neighbourhood and school environment. The findings suggest that after adjusting for various sociodemographic and familial factors, poor neighbourhood and school environments had the strongest associations with victimization including multiple types of abuse.¹¹ However,

this issue should be studied in more depth in future research in Malaysia.

TYPES OF REPORTED CHILD ABUSE OR NEGLECT

Physical abuse or non-accidental injuries

Intracranial haemorrhage is a major cause of severe morbidity and mortality in child abuse cases in developed countries. The earliest study in Malaysia looking specifically on intracranial haemorrhage amongst all cases of child physical abuse was published in 1994.²⁸ Among 369 cases of physical abuse treated in Hospital Kuala Lumpur over a 4-year period, 41 (11.4%) had intracranial haemorrhage, of whom 37 (90%) were 2 years old or less. A history of trauma was present in only eight (20%), of which only two were compatible with the injuries incurred. Subdural haemorrhages accounted for 80% of the cases, with skull fractures present in only nine cases. Fifty-four per cent of the 37 children aged 2 years of age or less had no external signs of trauma, but 11 of them had retinal haemorrhages. This is in contrast to the children older than 2 years of age who all had external signs of trauma. The overall prognosis was dismal with an early mortality of almost 30% (13 cases) and at least seven cases with severe neurological sequelae. These findings are comparable with studies from developed countries which have established that non-accidental injury must be considered as a cause of intracranial haemorrhage in any young child, despite the absence of external signs of trauma.

In another retrospective review reporting head injury cases between January 2005 and December 2006, there were 81 referrals for head injury to the Neurosurgical Unit at Hospital Kuala Lumpur.²⁹ Out of these, about half (53.1%) were suspected to be of non-accidental cause. The median age of the non-accidental head injury group was 4.9 months, with a significantly greater male preponderance (74%, $p=0.023$). This group of infants only represented those with head injuries severe enough for neuro-surgical intervention to be considered and thus did not include the milder cases of NAHI in the community who may have been misdiagnosed, e.g. as gastroenteritis or viral infection. Prevalence rates on NAHI thus cannot be drawn from this data. Features which could help differentiate accidental head injury from non-accidental head injury (NAHI) in infancy was conducted.²⁹ Lack of history of any injury that could lead to significant head trauma together with an acute onset of severe encephalopathy in a previously well child were two of these features. Accidental head injuries had been found to present early before worsening of symptoms or seizures whereas the non-accidental head injuries were more likely to present after status epilepticus or onset of encephalopathy. Delay in presentation has been described as a marker of child abuse. In the study above, 89.5% of 38 infants from accidental head injury were brought immediately for medical review as compared to a delay of more than 12 hours in seeking medical attention in 44% of the 43 infants in the NAHI group. Retinal haemorrhage was found in at least 58% of the NAHI infants. Only two of the accidental group had a retinal examination. The NAHI group was significantly more likely to have signs of increased intracranial pressure such as apnoea, vomiting, lethargy, limpness, irritability, seizures

and a Glasgow coma scale below 8 on admission compared to the accidental head injury group ($p<0.001$) or signs of prior minor illness that is, fever ($p=0.002$) and upper respiratory tract infection ($p=0.027$). On the other hand, those in accidental head injury group were more likely to have presented with parental concern after a fall or other consistently stated injury or facial or head swelling post injury ($p<0.001$). Subdural haemorrhages occurred more frequently in the NAHI group (88% vs 42%) whereas extradural haemorrhage was more frequent in accidental cases.

Sexual abuse or child neglect

There were no studies published which focused on the types of sexual abuse or child neglect, injuries sustained, pregnancy, profile of victims such as age of children, sites of abuse or profile of perpetrators. This data is available with the Social Welfare Department in view of mandatory reporting but there is no official publication. In local published studies on consequences related to sexual abuse, most were related to psychological and behavioural outcomes. Most of the published studies on sexual abuse in Malaysia are related to statutory rape.

Statutory rape and teenage pregnancy

Pre-marital sex and pregnancy outside wedlock are largely socially unacceptable in Malaysia and may be kept hidden from others. Many parents reported premarital sex in their children as rape because their teenagers initially report the sexual act as being against their will out of fear of parents' anger. It is also considered a statutory rape if the girl is below 16 years of age at the time of the sexual activity. The gap between age at first sexual intercourse and age at marriage has notably widened in many developing countries, with more young people sexually active before marriage than in the past. Malaysia faces a similar phenomenon. Mean age of premarital sexual activity was around 15 years.^{30, 31} An erosion of traditional and religious values were found in a survey of 389 Muslim adolescents in Malaysia and Indonesia on their sexual experiences, religiosity and a few youth cultural elements.³² Instead, peers and youth culture play a more significant role in their influence on engagement in premarital sex.

The prevalence of adolescents involving in premarital sex varied slightly depending to the age of the population under study. Generally, prevalence of premarital sex has increased and age of sexual debut has lowered. The recent Malaysian Global School-based student Survey (2012)² study involving students aged 13 – 17 years old reported about 8.3% school children had premarital sex, with male reported higher prevalence (9.6%) compared to female (7.1%). About one in every five students reportedly had their first sexual intercourse at age 11 years or younger. In Anwar et al's study involving adolescent respondents aged 15-20 years, a slightly higher prevalence of premarital sexual experience at 12.6% was found, of which 75.7% had their sexual debut at 15-19 years and 38.2% were having multiple partners (at least 3 partners).³⁰ Other studies also found that premarital sexual activity was significantly associated to gender, with males generally being more sexually active as compared to the females.^{31, 33} Nik Farid *et al* (2013) in her study amongst 1082

² http://www.who.int/chp/gshs/Malaysia_2012_GSHS_FS_national.pdf

incarcerated adolescents aged 12-19 years living in 22 welfare institutions in Malaysia, found that age of sexual debut was much earlier in this group with mean age at first sexual intercourse for both gender at 14.0 years old.³⁴ At the time of the interview, 62.3% had already initiated sexual intercourse at least once. Sexual abuse during childhood has the greatest influence on initiation of sexual intercourse, followed by permissive attitude towards premarital sex and use of substance abuse such as illicit drug and alcohol.

One exception to these findings, was a study that reported very low prevalence of pre-marital sex (4.6%) among 1328 youth trainees who were undergoing a national skill training programme at the time of the study. About 6.2% of the female trainees reported had pre-marital sex as compared to 2.6% of their male counterpart. The study also found that religion, race, having a partner, reading or watching porn, masturbation and bullying were related to premarital sex.³⁵ A comprehensive review on youth sexuality suggests that the method of obtaining the information related to sexual activity determines the reliability of the response since this is influenced by social and cultural sensitivity.³⁶

The continuing increasing prevalence of premarital sexual activity in this age group and the low contraceptive usage means increasing risk of rising number of teenage pregnancies. The recent increase in reports of abandoned babies has raised concerns about unwed teenage girls among the public as well as the policy makers. Adolescent mothers were significantly more likely to have a low educational level, to be unemployed, have a low socioeconomic status, being raised by a single parent, not engaging in extracurricular school activities, engaging in unsupervised activities with peers after school, and substance abuse. Teenage mothers are more likely to be anaemic, unsure of the expected delivery date, had few antenatal visits and late delivery booking; and low Apgar scores and more perinatal complications.³⁷ Adverse neonatal outcomes are also found to be more common in the newborns of nulliparous adolescents with a perinatal mortality rate of 14 per 1000 livebirths in mothers below 15 years of age and 7 per 1000 livebirths in those 15-19 years old compared to an average rate of 3 per 1000 livebirths in mothers aged 25 to 34 years old, according to the Malaysian Perinatal and Mortality report in years 2003 and 2004.³⁸ In a Canadian study,³⁹ the risk of preterm delivery was 4.5 times higher and risks of birth defects and infant death were 1.8 and 3.78 times higher in those newborns of nulliparous adolescents 19 years and below compared to the group of newborns of nulliparous women between 20 to 29 years of age.

Cyberbullying on internet and social networks

ICT-mediated communication is becoming an indispensable part of modern living, exposure to interpersonal violence related to the use of this technology is an unwanted consequence. A cross-sectional survey of secondary school students (n= 3426) in Selangor and Kuala Lumpur found that social networking was the most commonly reported purpose of Internet use. Online experiences of being bullied or harassed, receiving threatening messages and being invited to offline meetings with online acquaintances were not uncommon. Of those who received invitation to meet offline,

about one-third of them complied. About 26% of adolescents who went to these meetings found that the person they met was not a fellow peer as expected but actually an adult who gave a different profile while communicating online. Male gender, Malay ethnicity, online access at an Internet cafe, viewing pornography on the Internet, the absence of parental restrictions on visiting certain website and chat rooms, not being explicitly forbidden to meet strangers encountered online, and disclosure of personal information were significantly associated with increased odds of face-to-face meetings with online acquaintances. During such face-to-face encounters reported by 1,005 adolescents, 5.5% experienced either verbal, physical, or sexual assaults including 13 males and five females who reported forced sexual intercourse.⁴⁰

Another survey among secondary school users of social networking sites (SNS) in Negri Sembilan (n = 1364), found that more than half had experienced victimizations in the form of online aggression or unwanted sexual solicitation on SNS. Victimization was found to be higher in those who reported multiple risky behaviours online, especially engagement in online aggression towards others. In addition, offline experiences of bullying others, being a victim of abuse as well as high levels of parental conflict were found to increase the risk of online victimization.⁴¹

School bullying

In a cross sectional study of 12 year old school children in seven randomly selected schools in the Federal territory of Kuala Lumpur, the overall prevalence of those involved in bullying were 20% out of 410 recruited children; 2.4% were exclusive bullies and 17.6% were bullying as well as victims of bullying as assessed using The Malaysian Bullying Questionnaire. Male gender, attention deficit hyperactivity disorder (ADHD) as reported by the subjects or ADHD symptoms and conduct behaviour as reported by the teachers were found to be risk factors for bullying behaviour. There were no significant differences in the demographic characteristics of parents such as age, educational level, marital status and amount of time spent with children with regard to bullying behaviour. However the numbers of exclusive bullies in this study were small (n=10), and this was a self-reporting questionnaire.⁴²

PERPETRATORS

Many abused children, in particular sexual abuse, do not disclose the matter to the parents and/or authorities. Data suggest that from the cases being reported, the abuse often comes from someone within a trusted relationship. Choo et al in their study revealed that most perpetrators of physical abuse were adults (71.7%), with parents making up the largest group (39.9%). This is similar to data from SCAN team Hospital Kuala Lumpur and the Social Welfare Department. In addition, more than one quarter (28.3%) were peers. Thus, physical violence was experienced most commonly in the context of intra-familial victimization and bullying by peers. A substantial proportion of perpetrators were female (38.3%). Only 13.2% sought medical treatment suggesting a possibility of under-reporting. On sexual abuse, adult males (42.9%) were the largest group of perpetrators of

acts involving contact and penetration, most commonly male friends and relatives. Male peers (30.6%) were predominantly boys in the neighbourhood and friends outside school. Approximately one-quarter of perpetrators of sexual victimization were females, equally split between adults and peers. The largest groups were adult friends and peers outside school with little evidence of intra-familial sexual victimization by females. Overall, 44.6% of respondents who reported contact sexual victimization nominated more than one perpetrator. Only a small proportion of perpetrators were "unknown".¹¹

Traditionally, parents depend on the extended family to provide care for children. A study on Childcare and Parenting Styles among Working Parents in Malaysia conducted in 1998 by the National Population and Family Development Board found that working parents rely on family members to care for their children with grandparents (60.4%) playing a major role.⁴³ However, there is a growing use of domestic servants (6.6%) for childcare with many coming from Indonesia and the Philippines, while about 9% of the children have no caregivers while their parents work outside of the home. Notably, a study based on reported hospital cases found that some children suffered both physical and sexual abuse while in the care of the child minders.^{44,45}

The majority of perpetrators of non-accidental head injuries in infants have been suspected to be their child minders. In the study by Thalayasingam et al (2012), most of the infants were symptomatic at the time the infants were with home-based child minders, 60% of whom could not give any explanation as to the head injury.²⁹ Home-based childminders and workers in nurseries in urban areas generally do not have formal training in child development and some are caring for more than one infant or toddler at the same time.⁴⁶ Under the recently reviewed Akta Taska 1963, the only requirement with regards to child care and knowledge in child development as part of the registration to be a home-based childminder is to attend a one-day course on basic child physical care.

In Kelantan, a study conducted on cases of sexual offences seen in the One Stop Crisis Centre (OSCC) in Hospital Universiti Sains Malaysia (HUSM) from the year 2000 to 2003,⁴⁷ there was a total of 439 reported sexual offence cases. Slightly a quarter (26.4%) of these cases were children of ages 0-12 years of age where the perpetrators were relatives in 49% of these children. The majority (61%) of sexual abuse survivors attending the OSCC in HUSM were adolescents and their perpetrators comprised a known person(s), 70% being boyfriend or acquaintance and 20% a relative. This study exemplifies the finding in most child sexual abuse literature that the majority of perpetrators are known to the child sexual abuse survivors. One hundred and twenty cases of child sexual abuse (27.3%) to this referral centre were incestuous in nature, ranging from survivor's grandfather to their cousins.

There are also reported incidents of sexual abuse which involve individuals in position of power. In particular, one case report on sexual abuse of an adolescent girl perpetrated by a purported religious leader-cum-traditional healer illustrated how she had been sent to a "religious" person after

she had dissociative symptoms only to be sexually abused by the "religious healer".⁴⁸ Her parents had not taken the actions of the "religious" person as sexual abuse, even though the girl had disclosed that she had been fondled and digitally penetrated, but encouraged her to continue the "healing rituals" for another week. She only received psychotherapy and antidepressant after another relative reported the abuse. This is not an unusual case where adolescents or women are sexually abused in the guise of traditional treatment (from news reports) but there is no prevalence data on such incidents to determine the size of the problem.

MANAGEMENT

Management of the abused child involves looking at child safety such that to prevent further abuse as well as that related to the rehabilitation of the child and/or family. The agencies involved in child safety are the social workers who are gazetted as Child Protectors under the Department of Social Welfare and the Police. There are multidisciplinary teams called Suspected Child Abuse and Neglect (SCAN teams) and One Stop Crises Centres within hospitals where the health workers attend to emotional, psychological and physical health needs of the child, psychodynamics of the family. The police and legal agencies focus into legal protection of the child and prosecution of perpetrators. In addition there are dedicated police units in the major towns to attend to children suspected to have been sexually abused.⁴⁹ There are no published studies in Malaysia auditing the accessibility and effectiveness of these services. Unlike medical illnesses, abused children are usually dependent on the perpetrator to access such services resulting in high default rates unless there is legal compulsion. There are no papers evaluating the role of Courts in ensuring access to rehabilitation services by the parents or guardians or audit on the effectiveness of rehabilitation or incidence of repeated abuse or neglect.

TREATMENT

Of the studies examining factors that influence the survivor's experience of sexual abuse, one qualitative study by Ping and Sumari (2012) looked at the element of spirituality in the healing experience from sexual abuse amongst seven women survivors.⁵⁰ Inclusion criteria were women aged at least 21 years old, had at least 2 episodes of sexual abuse in one year and considered themselves healed or in the process of healing from sexual abuse. In this group of women survivors, they utilised positive spiritual coping to gain inner strength and love to overcome past trauma and they used spiritual prayers and readings to gain calmness and peacefulness, enabling the survivors to experience less anger and less likely to develop depression. Women with negative spiritual coping perceived sexual abuse experience as being a punishment from God, thus suffered from greater negative impact. The study highlighted the need for awareness of professionals and researchers that the effect of spiritual coping depends on the type of spiritual coping used and not to assume that all spiritual copings will have a positive impact and further research was required to look at intervention frameworks to assist survivors' healing from sexual abuse through spiritual means.

One literature review of publications by Muslim and Western scholars on school violence and juvenile delinquency was conducted by Ismail and Rahman (2012).⁵¹ It was emphasised that in the eleven relevant publications, the psychologists focused more on the behavioral, biological, social, family, and cognitive as the preventative methods of reducing school violence and juvenile delinquency without paying much attention to the human spirituality. It was found that there were limited studies done from the Islamic perspective to develop, test, and deliver evidence-supported intervention focused on juvenile violence and the authors exhorted on a need for such studies as this was a potential treatment intervention in a Muslim predominant country like Malaysia.

Husain and colleagues (2009) interviewed 65 Malay female aged between 8 to 17 years seen in the OSCC Hospital Universiti Sains Malaysia from June 2005 to March 2006 within 6 months of the initial attendance. Sixteen (25%) of participants were found to be depressed using the Children Depression Inventory.⁵² Incest cases were excluded in this study with the majority of perpetrators being boyfriends or close friends. Using semi-structured questionnaires and descriptive evaluation, the investigators found that 59 participants (90.8%) used emotion-focused strategies and 6 participants (9.2%) used problem or task-focused strategies. Among emotion-focused coping strategies, participants coped by deciding that nothing could be done to change things, were in denial, or suppressed their feelings. The authors postulated that such strategies were chosen probably due to cultural issues and beliefs that sexual abuse was a taboo subject and not to be disclosed. Avoidant strategy, although viewed as less effective, was thought to be a practical and helpful coping strategy in our cultural context of feeling of lack of control and helplessness experienced by survivors of sexual abuse, especially in school. More infrequently used was problem focused coping strategy, the most utilised type was the use of positive interpretation. Having a confidante was a protective factor against depression in this study. The incidence of depression was significantly associated with a duration of less than 28 days after the presentation for sexual abuse at the time of the interview. However, the authors opined that emotion-focused strategies such as avoidant coping although seemingly beneficial in the short term may be more harmful in terms of long term and negative psychological effects, as compared to expressive coping.

Lack of knowledge among health care providers in the management of domestic violence may also impact on the holistic management of physical abuse if they only attend to aspects of child physical abuse but not to domestic violence which may be present concurrently. In one survey, all clinicians and nursing staff of the outpatient, casualty and antenatal clinics in University Malaya Medical Centre (N=188) reported using a self-administered questionnaire (53). Sixty-two percent of the clinicians and 67% of the nursing staff perceived the prevalence of domestic violence within their patients to be very rare or rare. Time factor, concern about offending the patient and unsure of how to ask were reported as barriers in asking for domestic violence by 66%, 52.5% and 32.8% of the clinicians respectively.

Victim-blaming attitude existed in 28% of the clinicians and 51.1% of the nursing staff.

OUTCOME

Psychological and behavioural

It is well documented that abused children experience psychological problems such as depression, anxiety, regressive or withdrawal behaviours, self-harm, post-traumatic stress disorders in prospective studies.^{54, 55} Specifically, reviews have suggested that survivors of child sexual abuse are significantly at risk of a wide range of medical, psychological, behavioural, and sexual disorders. Prospective studies have shown that child abuse especially sexual abuse carries negative psychological consequences into adulthood.⁵⁶ The effects of sexual abuse may vary with the gender, type and extent of abuse, the extent of force involved, the age of the victim, the relationship with the perpetrator, resilience of the child and how the family and society treat the abuse. The more severe the sexual abuse in terms of degree of sexual contact and the closer in relationship between the child and perpetrator, the greater the impact of the sexual abuse on mental health according to many of the publications in the developed countries.⁵⁷⁻⁵⁹

In a cross-sectional study of 51 females aged ranging from 12-20 years who were referred to the SCAN team in Kuala Lumpur Hospital for 'sexual abuse', the severity of the sexual abuse did not correlate with the presence of depression, but rather correlated with living away from the parents.⁶⁰ Sixty-eight per cent of the girls were below 16 years of age and referred for statutory rape and thus not as traumatised by the consensual sexual contact. Thirty percent of the participants were found to be depressed using the *Strength and Difficulty Questionnaire (SDQ)*, *Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS)* and *K-SADS-PL (Present and Lifetime version)*, diagnostic tools for assessment of depression. Living away from parents, rather than the severity of the sexual abuse was the sole predictor of depression in this group. Good family support is thus important to reduce the impact of sexual abuse on adolescents, as is the avoidance of sending them to live with others after sexual abuse to avoid stigma. It was not clear from the study whether the girls were living away from the parents prior to or as a consequence of being sent to live with family members or institutions after the sexual abuse. This has implications in mental health outcome in sending sexually active adolescents to institutional care when they are deemed to be "beyond control". Counselling, detection of depression and psychological management is important in children who are sent away from home after disclosure of sexual abuse or statutory rape.

One adverse outcome of child abuse is substance abuse and resultant incarceration as found in a study conducted in 2010 by Ahmad and Mazlan (14). They studied the relationship between substance abuse and childhood trauma experiences defined as experiences of various types maltreatment before the age of 18 years. There were four groups of study participants, i.e. 123 incarcerated boys and girls from detention schools under the Malaysian Prison Department and 642 non-incarcerated boys and girls with ages ranging

from 15-20 years and no prior history of past conviction or physical or mental health problems. The instruments used were a screening instrument to assess alcohol and drug use, and a Childhood Trauma questionnaire. The prevalence of substance abuse and childhood trauma experiences are higher among incarcerated youth compared to the non-incarcerated youth. In addition, it was found that childhood trauma, particularly abusive rather than neglectful experiences, significantly contributed to substance abuse among incarcerated girls but not boys. These findings are potentially useful to provide empirical knowledge for designing rehabilitation programmes for incarcerated youth.

Children who have been abused and thought to be unsafe to be left in the care of their family are often placed in residential care. In 2009, 1127 children were reported to have been placed in welfare homes run by the Malaysian Social Welfare Department and 74 children placed in foster homes.⁶¹ Reasons for care included abuse and neglect, family dysfunction, disability, parental illness or disability, low income, at risk of significant harm, challenging behaviour or beyond parental control and criminal offences. This study by Abdul Rahman *et al* (2013) was a comparative cross-sectional study comparing school-going residential care children aged 7-12 years from one such welfare institution with a control group of school classmates living with at least one birth parent and had no previous history of contact with the Social Welfare Department. The child/ carer ratio varied from one carer to 11 children to one carer to 20 children and the carers changed from one day to the next. Out of 53 residential care children from one centre and 61 control classmates, the former group had significantly higher scores on the rule-breaking ($p < 0.001$) and Diagnostic and Statistical Manual of Disorders (DSM) conduct problem scores ($p < 0.001$). Rule breaking, DSM conduct problems and externalizing scores were positively correlated with duration of stay. Abuse and neglect cases which comprised two-thirds of the 53 children had higher anxiety and depression scores ($p = 0.024$). The number of reasons for residential care of each child positively correlated with several subscales. As the questionnaire were completed by the carers, the authors considered the possibility that externalized behaviours may have been more easily detected by the carers as compared to internalised behaviours such as withdrawal.

The association of childhood adversity with depression was explored in 52 adult depressed patients compared to 52 controls matched for age and sex in a Malaysian population. There was a positive relationship between childhood abuse in general and childhood physical abuse with adult depressive disorder.⁶² Nearly a quarter (23%) of depressed patients reported being abused in childhood compared with none in the control group. There was no significant association between childhood loss and depression in adulthood. Low level of parental care during childhood was significantly correlated with adult depressive disorder. Mental health professionals should explore past history of childhood abuse or neglect including poor parental attachments in all depressed patients.

The link between childhood abuse and prostitution in Malaysia was demonstrated in a study involving semi-

structured interviews and narrative interviews of 63 young women safeguarded from prostitution in two rehabilitation centers.⁶³ Half of them were sexually abused during childhood before being drawn into prostitution. Sixty-seven percent (67%) of respondents had suffered multiple types of abuse and at the time of the study had negative feelings of hurt, anger, revengeful, depression, isolation from family and low self-esteem.

A qualitative study looking at 10 female adolescent incest victims illustrates some of the risk factors and protection issues associated with incest i.e. dysfunctional families, mothers not being home much of the time due to financial difficulties, threats and coercion from the perpetrators as found in most sexual abuse, lack of support from mothers who are more protective of the fathers after disclosure and being displaced from home due to stigma.²² Out of these 10 victims, 5 suffered emotional trauma with 3 having tried to commit suicide. None of the perpetrators in this group had been successfully charged and prosecuted for incest. Perpetrators may not be successfully prosecuted because of the pressure on the incest victim to recant and reported cases.

Mortality

There have been no recent published studies looking directly at childhood deaths from non-accidental injury in Malaysia. One particular published work dated back to 1995 by Kasim and colleagues.⁶⁴ They reported the major cause of death due to child abuse was subdural haemorrhage in 17 out of 30 fatal cases of suspected child abuse reported from 1985 to 1991. Other causes were due to blunt abdominal trauma, septicaemia from inflicted burns, drowning in river in infants, strangulation and poisoning.

In the Federal Territory of Putrajaya, 33 infants were reported as brought-in-dead from home-based nurseries for the years 2007-2009.⁶⁵ Only 40% had post mortem were performed. The deaths were attributed to be due to non-accidental head injury, asphyxiation or aspiration. Of the 56 cases who were brought to Putrajaya Hospital then, 16 cases who were infants (28.6%) had intracranial haemorrhage. More publications are required on NAHI in terms of true incidence and risk factors as this is an important cause of significant morbidity and mortality in infancy from child abuse. Without post-mortem examination in many of these unexpected infant deaths, especially in those brought-in dead, deaths from NAHI may be under-diagnosed. Some of these infant deaths could also be due to suffocation, accidental or otherwise.

Accidental childhood injuries or death could also be seen as a form of child neglect. A case report⁶⁶ of an 11-month old found drowned in a half filled pail in the toilet of a nursery was reported by pathologist Faridah and Khariani in the year 2003 to highlight the case as that would probably have been charged as neglect in the United Kingdom since it was a 'breach of the duty of care' and that strict regulations for nurseries and proper supervision of the children should be imposed.⁶⁶ There is no data published on accidental drowning in toilet or bucket deaths, preventable deaths which can be attributed to neglect or lack of awareness of risks by the carers. Similarly, there were 14 cases of fan blade

injuries, an otherwise rare accidental injury, referred to the Neurosurgery Department in Hospital Kuala Lumpur in the year 2000 alone,⁶⁶ due to children jumping on the upper bunk bed placed near ceiling fans and 2 cases of children being lifted by an adult in play. In a cross-sectional survey of infant sleep and care practices conducted among parents of babies aged below 8 months,⁶⁷ 24.7% of 263 infants were placed to sleep in the non-supine position. The most common modifiable risk factor for Sudden infant death syndrome (SIDS) was the presence of soft toys or bedding in the infants' bed or cot (89.4%).

Prevention

A recent systematic review of reviews revealed a significant imbalance in the distribution of child maltreatment prevention research. Low- and middle-income countries contributes only 1% to this body of evidence.⁶⁸ There is a lack of epidemiological data on effectiveness of policies and programmes preventing child maltreatment and a particularly large research gap between developed and developing countries. Malaysia is of no exception, with very limited data on what works in the local context.

In a multi-countries' study to assess prevention programmes on CAN implemented in various countries, Cheah and Choo (2013) found that Malaysia scored a moderate (44%) overall readiness score according to WHO child maltreatment prevention readiness assessment tool.⁴⁹ Whilst there is scientific data and some knowledge of child abuse prevention and strong legislation and policies for child abuse tertiary prevention, Malaysia was under-resourced in human and technical resources as well as there being a lack of focus in programme implementation and evaluation by the policy makers and gaps in the delivery of services. Majority of survey respondents from both government and non-government bodies felt that the public did not perceive child abuse as a major problem and could be controlled by legal deterrents. Programmes to promote stronger families and prevent child abuse are listed in the publication. In order to attain political will to tackle the problem, there should be a repository of data related to child abuse as in a national clearing house, more studies to determine risk factors and high risk populations to provide focus for large scale implementation. Large scale universal programmes for prevention would largely involve the public health, education and welfare sectors in which there should be training of staff dedicated to the delivery of prevention services. Child abuse prevention requires multi-sectoral and multi-agency networking and linkages and the recommendations are to formalise and systematise collaboration between government agencies and NGO's, religious organisations as well as corporate sectors in their corporate social responsibility role.

Prevention and management of child abuse cannot be seen in isolation from other social issues faced by the parents or family. In the study on victimisation experiences on adolescents in Selangor,¹¹ of the 1870 adolescents 10% reported witnessing parental domestic violence, 4% reported parental alcoholism, and almost 2% reported parental mental illness. Reports of parental drug use were very rare (0.2%). In this study, adolescents exposed to domestic

violence or parental alcoholism were, respectively, two and three times more likely to report physical and sexual victimization. Resources have to be placed to address these social issues as part of the prevention of child abuse in the community.

Under the Child Act 2001, doctors, family members and nursery workers are mandated to report child abuse or neglect. There is no available study regarding the impact of mandatory reporting in Malaysia. One advantage is having epidemiological data available and to be compiled by a statutory body like the Social Welfare Department and bringing the cases to the attention of officers with legal clout. However, mandatory reporting does have its controversies depending on the effectiveness of prompt assessment, rehabilitation, protection and prosecution after reporting.

Mandatory child abuse and neglect reporting laws apply to teachers in many countries of the world. However, such laws have not yet been introduced for teachers in Malaysia, and there is debate about whether the laws should be extended to teachers at all. Choo and colleagues (2013) investigated the level of support to assume mandatory reporting duties among 668 randomly selected teachers.⁶⁹ Results showed that 44.4 percent of the respondents supported legislation requiring teachers to report child abuse. Teachers do not unanimously support the introduction of mandatory reporting legislation for teachers in Malaysia, and there is a lack of clarity about what such laws will mean for teachers. This study provides important insights into factors influencing teachers' support. Teachers of Indian ethnicity, those with shorter duration of service in teaching (less than 5 years), availability of a knowledgeable and supportive school staff, and higher level of commitment to reporting were significant factors affecting teachers' support for mandatory reporting. Specific training programs are needed to raise teachers' awareness, build their confidence and enhance their willingness to report child abuse.

"Safe touch" programs have been used in developed countries to teach young children to inform parents early if touched inappropriately before the further progression of sexual abuse. In a study looking at personal safety teaching to 9 year-old school students in five schools, featuring games and role play to teach children about potentially unsafe situations and touches, and to teach children how to say "no, run and tell", it was found that there was substantial gains for two-thirds of the personal safety curriculum but some students still could not grasp the concept of reporting inappropriate touches by an adult to a trusted adult.⁷⁰ There are no publications of the effectiveness of such programs or the difficulties in implementation of such programs in kindergartens or preschool setting.

Adolescent sexual and reproductive health (SRH)

This topic is considered relevant in the prevention of child abuse and neglect in view of the risks of statutory rape in adolescents due to lack of knowledge on what constitutes statutory rape. In addition to having unplanned pregnancies after casual sex, the girls are at risk of domestic violence from their husbands who may have felt forced to marry to avoid a jail sentence. Majority of the studies that were conducted on

adolescent sexual and reproductive health (SRH) in Malaysia were largely focused on adolescents' knowledge on SRH or HIV issues, premarital sex and teenage pregnancy. Most studies examined factors on the issues which focused primarily on the individual level, although an increasing number of studies within the past decade have focused on family-level or school factors. None of the studies examined factors at the community or neighbourhood level, which, to date, has largely been ignored.

Several studies conducted highlighted the lack of knowledge among Malaysian adolescents in SRH issues.^{71,72} For instance, Ab Rahman et al (2011) in their study among 1035 secondary school children in Kelantan found that 69.6% respondent did not think that one may get pregnant after a single act of sexual intercourse, only 12% of them correctly responded to the statement regarding sexual intercourse being a cause of sexually transmitted infections (STIs). Although some students were aware that pregnancy can be prevented using condom (60%), misconception about sexual intercourse and pregnancy still prevailed then, where approximately 17% of the students thought that washing the vagina or having a hot shower after sexual intercourse could prevent against pregnancy. Very few students obtained information about sexual health from their teachers (17.2%) and parents (6.5%), whilst peers (64.3%), mass media (60.2%) and internet (53.6%) played a major influence on their sexual information seeking behaviour.⁷¹

In a study by Zulkifli and Low (2000) examining premarital sexual practices amongst 468 unmarried participants aged between 15-20 years found 13% of them reported early sexual experience and found that living away from parents and family were significantly associated with higher rate of early sexual experience.³³ A more conservative attitude towards promiscuity, infidelity, casual sex or engaging in sex with prostitutes was found in those without sexual experience. Seventy-two percent of those who had sexual experience had not used any contraception on first intercourse. Pregnancy in adolescents or unmarried young adults are less likely to be wanted and these newborn babies are at risk of abandonment. The authors stressed that sex education should be made available and focused on risks from sexual activities, as an integral part of schooling, with support from parents and the community. From the findings of the study, courses clarifying and educating on sexual values and decision-making skills may prove useful in delaying sexual activity. This may help to reduce cases of statutory rape and the attendant problems of teenage pregnancies.

The most basic rights of adolescents in sexual reproductive health is to obtain accurate and complete information about their body functions, sex, safer sex, reproduction, consequences of STIs and early pregnancy in order to build life skills for inter-personal communication and decision making in sexual matters. Without accurate information, adolescents are likely to make poorly informed decisions that may have profound negative effects on their lives. However, a qualitative study conducted among boys echoed earlier findings that their knowledge on safe sex was still vague (73). While the interviewed boys perceived themselves to be at risk

of HIV infection, they admitted their lack of skills in handling these issues. Sources of sexual information were mainly from male friends or through the mass media, and none of their parents talked to them about sexual matters.

The effectiveness of sex education programme in reducing adolescent sexual risk behaviours and promoting sexual health has been shown in literature elsewhere. In a review on the effect of 83 evaluated sex education programmes on one or more of five sexual behaviours: sexual initiation, frequency of sexual intercourse, number of sexual partners, condom use, and contraceptive use, showed substantial evidence that curriculum-based programmes can have positive effects on risky sexual behaviours in young people. About two-thirds (65%) of the studies found a significant positive effect on one or more reproductive health outcomes; only 7% found a significant negative effect.⁷⁴ However, the effectiveness of sexual health education in Malaysia remains to be tested. Findings from a recent study amongst 1706 university students aged mainly between 18-19 years suggests that recollection of sexual health education previously taught in school was low.⁷⁵ Most recalled having learnt about "sexual and reproductive systems" (69.4%) followed by "puberty" (65%) and the least (58.8%) on "relationship with the opposite sex". More than 80% of respondents requested more in-depth information to be taught regarding STIs, HIV, body development during puberty, sexual respect and reproductive health topics. The study found that although the program prescribed was the best for teaching a culturally sensitive topic, there remains significant gaps of what was actually received at ground level. Monitoring efforts have revealed that teachers either shy away from the teaching this component or are themselves not skilled and not trained to deal with such a sensitive subject.³⁶

Research tools related child maltreatment

Several instruments has been tested and piloted to measure several aspects of child abuse in Malaysia. The ISPCAN Child Abuse Screening Tool—Retrospective (ICAST-R) questionnaire was developed to gather retrospective self-report information regarding abuse and neglect by adolescents or young adults.⁷⁶ The ISPCAN Child Abuse Screening Tool - Parent Version (ICAST-P) has been developed as a survey instrument to be administered to parents for the assessment of child maltreatment.⁷⁷ Other recently developed tools include the Readiness Assessment for the Prevention of Child Maltreatment methods to assess countries' readiness to implement evidence-based child maltreatment prevention programs on a large scale,⁷⁸ whilst the Teacher's Reporting Attitude Scale (TRAS) is a tool to assess teachers' attitudes and willingness toward reporting child abuse and neglect.⁷⁹

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

This review has provided an insight into the substantial research gap on child abuse and neglect in Malaysia. There are a few studies in schools with larger sample size but the majority of local published studies are localised to single centre studies and small numbers making strong conclusions difficult especially in this area of study which have many confounding variables. Incidence of child abuse and neglect

is collected nationally but available only upon request from the Social Welfare Department and the Police. Large epidemiological data especially prospective cohort studies and social anthropology studies looking comprehensively at risk factors including resilient factors that protect the child from the effects of child abuse remains lacking.

There is no local published research looking at the public perception of child abuse and there is usually a gap between that and the actual reality. There are no local studies focusing on the impact of emotional abuse which is commonly associated with other forms of child maltreatment but often not reported or classified as concurrently present with physical abuse or neglect. By having local data regarding public perception of child abuse and neglect, social marketing campaigns can be a valuable tool for informing the public and policy makers to advocate for prevention and care services and appropriate law reform.⁸⁰ When physical abuse or sexual abuse is depicted as only the type at the severe scale, parents may not be aware that their corporal punishment can be abusive or that inappropriate touch is sexual abuse.

A database on fatality or injuries from supervisory neglect, deprivation of needs and medical neglect is currently not available. Under 5 mortality reports presently collected should be systematically compiled to look at child fatality from supervisory neglect or medical neglect. Supervisory deaths include deaths from unintentional drowning in bathrooms or home pools, accidental poisoning, being knocked down on reversing vehicles, sudden death in homes or child care centres. Medical neglect include late presentation for medical treatment or psychiatric neglect leading to suicide. Research into incidence and types of fatal neglect, risky parenting and a review into what is the line between accidental death and that caused by lack of appropriate supervision according to the age of the child is important to develop effective preventive measures.

The majority of studies on sexual abuse involve adolescence and there is no differentiation between the outcomes in consensual sex in statutory rape as compared to actual sexual abuse. In addition the lack of knowledge about sexual reproductive health amongst Malaysian adolescents suggests the need to strengthen the SRH education programme in schools. As the school setting is an ideal one for promoting adolescent health and for building gender sensitisation, the challenge is to review teaching methodology, skilled persons to teach and fully utilise the school based program.^{36, 75}

Abused children placed in welfare institutions were found to have higher anxiety and depression scores.⁶¹ It is important to continuously screen and examine the mental health status of residents in statutory residential care especially involving those coming from abusive homes or experienced child abuse and neglect, as well as monitoring behavioural problems arising from prolonged stay in institutional care or lack of appropriate rehabilitation.

SECTION 3: FUTURE RESEARCH DIRECTION

Prevalence studies are more useful than incidence studies in the field of child abuse and neglect. Unlike medical diseases,

the incidence rate is not the real rate due to reporting patterns. This is particularly so in intra-familial abuse especially incest where reporting may happen only years later. In addition to epidemiological data that could be published by the Social Welfare Department, prevalence or incidence studies could focus on various types of abuse other than physical or sexual such as emotional abuse, various neglect, cyberbullying, school bullying, exposure to pornography or domestic violence, as well as deaths from physical abuse, non-accidental head injuries or neglect including those from 'accidental' home injuries, and study risk factors for each type of abuse or neglect in greater detail to better enable effective prevention work.

For outcome data, studies looking at prevalence of child abuse or neglect in adults and comparing to health and social outcomes as described here could be done on a larger scale. The burden of child abuse ranging from physical and mental health cost, reproductive, legal, police work, prison, social work, public property damages, shelter home costs is important to raise awareness of the societal effects of child abuse and neglect. Information regarding institutionalised children and their outcomes needs to be collected prospectively to evaluate its effectiveness and identify any weaknesses in the system.

More studies in our local context as to the type of psychological treatment or domestic violence counselling, the impact of various forms of rehabilitation or relief of social stressors, as well as the topics mentioned in the previous sections, are required. Furthermore, many children do not receive long term assessment and follow-up as they are dependent on their parents to bring them for review. Child sexual abuse has been shown in almost every country to be strongly linked to poor mental health and self-harming behaviour and this may not necessarily be obvious at the outset.

Research in the area of sexual abuse should separate statutory rape cases (a legal definition based on age of consent in the case of consensual sexual contact) from those cases where the sexual act is abusive i.e coercive or forced. Emotional trauma from the former is more likely to arise from the events post discovery such as system abuse after reporting and any non-supportive reactions or actions of family members and the community. The degree of trauma from consensual sexual contact in statutory rape results from the effects of reporting rather than the sexual act.

Evaluation studies on sexual reproductive health education programs, rehabilitation programs including those on perpetrators, prevention programs including public health ones or outreach and reporting systems such as Child Help line or Talian Nur, could help policy makers determine the allocation of resources for those found to be effective and reproducible. Qualitative studies especially in mental health programs are equally as important.

Effectiveness of treatment programs are affected by the perception, knowledge and attitudes of professionals working in the field and whilst reporting and prevention programs are affected by what is defined as child abuse or neglect by public and professionals. Research could be designed to look into

factors which hinder reporting of child abuse, actions taken by the professionals and hindrances to effective handling and rehabilitation of reported cases.

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A Review of Occupational Injury Research In Malaysia

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ABSTRACT

A literature review of 16 papers on occupational injury research in Malaysia published during a 13-year period from 2000-2013 was carried out. The objective of this review and article selection was based on relevance to the research theme and mention of areas for future research. Most of the publications have focused on descriptive epidemiology, management practices, worker's knowledge, attitude, training, and rehabilitation services. The transportation, agriculture and construction sectors were found to be the most hazardous sectors and would benefit the most from Occupational Safety & Health (OSH) research and interventions. There is a strong need to develop a national injury surveillance system and also a mechanism to ensure adherence to the Occupational Safety & Health Act(OSHA) 1994. Detailed description and identification of risk factors for occupational injury in the environment, including machinery and equipment used was generally lacking. Future research on occupational injury should focus on surveillance to determine the magnitude of occupational injuries, determination of risk factors, identifying cost-effective interventions (such as enforcement of OSHA regulations), and assessment of rehabilitation services. Relevant government agencies, universities, corporate sector and occupational safety organizations need to play a proactive role in identifying priority areas and research capacity building. Funding for occupational injury should be commensurate with the magnitude of the problem.

INTRODUCTION AND METHODS

The Organization for Economic Co-operation and Development (OECD) defines occupational injury as "Any personal injury, disease or death resulting from an occupational accident". Worldwide, there are about 100 million cases of occupational injury each year,¹ resulting in 350,000 deaths.² Developing countries have the highest injury fatality rate.^{3,4} Occupational safety and health is important for moral, legal and financial reasons. We identified all publications on occupational injury research in Malaysia from year 2000 to year 2013 through a database dedicated to indexing all original data relevant to medicine in Malaysia using the medical subject heading (MeSH) Occupational Injuries.⁵ Sixteen publications were selected for inclusion in this review based on relevance to the research theme and mention of areas for future research.⁵ A summary of the findings and recommendations was made. The objective of this review article is to summarize what has already been published in Malaysia on Occupational

Injuries, to identify gaps in knowledge, policy and to explore potential areas for future research.

SECTION 1: REVIEW OF LITERATURE

Occupational Injury Prevention, Surveillance and Rehabilitation in Malaysia

In Malaysia, the Department of Occupational Safety and Health (DOSH) under the Ministry of Human Resource is responsible for enforcing the law on occupational safety and health, which was introduced in 1994. The Occupational Health Unit conducts surveillance activities. The notification of occupational poisonings, diseases and injuries is done by hospitals and clinics within the Ministry of Health. Malaysia's Social Security Organization (SOCSO), also known as *Pertubuhan Keselamatan Sosial* (PERKESO), was set up in 1971 to provide socioeconomic security for non-government employees. The Employees Social Security Act 1969 mandates all employers to insure their employees for workplace diseases or injuries by contributing to PERKESO. Data obtained from PERKESO are more comprehensive than those obtained from Malaysia's Department of Safety and Health.⁶ Up till 2006, PERKESO covers 67% of total formal workforce within Malaysia.^{7,8} PERKESO provides employment injury insurance schemes, disability benefits, rehabilitation programs and certified training programs for disability assessment (CMIA).

Workers compensation for injury is provided by both the government and private sectors. The Persons with Disability (PWD) Act 2008 empowers PWDs to obtain various privileges such as the right to special barrier-free access to public facilities. The Labor Department has various vocational programs for the employment of PWDs.

PERKESO introduced the Return-To-Work program(RTW) in the year 2007 to rehabilitate workers suffering from injuries to achieve their maximum functional capacity at work. The RTW process can be divided into 4 phases: (i)Off duty, (ii)Re-entry, (iii)Maintenance and (iv)Advancement. The RTW programs are managed by the Ministry of Human Resource.

Epidemiology

Aidinegara *et al.* conducted a secondary data analysis of the PERKESO database to examine the fatal occupational injuries in Malaysia.⁷ This refers to the death of an employee in the workplace as a result of any injury occurring during employment. This also included death occurring outside the

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workplace while performing official duties as an employee. This analysis had revealed a total of 2822 fatal occupational injuries with an average annual incidence of 9.2 fatal occupational injuries per 100,000 workers. This figure is higher than that in the United States (4.0 per 100,000 [US Bureau of Labor Statistics, 2006]) and Great Britain (0.71 per 100,000 [Health and Safety Executive UK, 2006]). From the year 2002 till 2006, there was a 16% decline in the annual number and 34% decline in the annual incidence of fatal occupational injury. Older workers in the 60+ and 50–59 age groups had the highest incidence of fatal occupational injury. Indians had the highest average annual incidence compared to Malays or Chinese (17.6 vs 8.7 vs 8.1 per 100,000 workers). Men had a 12 times higher annual average incidence compared to women (13.8 vs 1.2 per 100,000 workers) and the authors suggested it is probably because men are more likely to have high-risk jobs. The transportation sector reported the highest incidence (35.1 per 100,000), followed by the agriculture (30.5 per 100,000) and construction (19.3 per 100,000) sectors. These accidents involved transport and lifting equipment (53%), working-environment (22%) followed by machines (5%). The most common fatal occupational injuries were fractures (15%), unspecified wounds (8%), concussions and internal injuries (6%), and contusions and crush injuries (4%). The main causes of these injuries were falling from height (28%), being struck by moving objects (17%), and struck by falling objects (9%).

Adinegara *et al.* also conducted a secondary data analysis of the PERKESO database to study the non-fatal occupational injuries in Malaysia.⁸ Between the years 2002–2006 there were a total of 249,904 non-fatal occupational injuries occurring in 211,875 individuals. There was a decrease in both annual number and annual incidence by 37% (62,737 to 39,366) and 51% (11.4 to 5.6 per 1000 workers [p trend < 0.001]) respectively. The agriculture sector had the highest incidence (24.1 per 1,000), followed by the wood-product manufacturing (22.1 per 1,000) and non-metallic industries (20.8 per 1,000). Highest incidence was seen in the 40–49 year age-group (7.9 per 1000) followed by the 30–39 year age-group (7.5 per 1000) and 19–29 year age-group (7.4 per 1000). Those more than 60 years of age had a lower incidence. The authors suggested that these employees were probably stationed in senior positions which are at a lower risk. Men had a higher average annual incidence (10.7 per 1000) compared to women (3.6 per 1000). Indians had the highest average annual incidence (21.1 per 1000) followed by Chinese (8.9 per 1000) and Malays (6.8 per 1000). Most common injuries were unspecified wounds (55%), superficial injuries (10%), fractures (10%), strains and sprains (7%), concussions and other internal injuries (4%), contusions and crush injuries (4%), dislocations (2%), burns (2%), and amputations (2%). The main causes of these injuries were being struck by moving objects (33%), falling from height (19%), and trapped between objects (17%). These injuries resulted from accidents from within the working-environment (41%), during handling of machines (20%) and during exposure to materials and substances (12%).

There were several limitations Adinegara *et al.* noted in the PERKESO database.^{7,8} The database was set up for monitoring the total number of employee related claims/benefits and

was not specifically designed for surveillance. The database does not include data from all categories of employees. Data from four categories of employees are excluded, namely: self-employed, foreign workers, government employees and domestic servants. About half of the reported injuries (47%) were classified as “unspecified”, meaning there is no specific classification suitable for these cases. Though a worker could have died of multiple injuries, only one entry is allowed for classification of injuries. The database does not contain data from certain industries such as mining and quarrying. The database has a risk of under-reporting less severe injuries because willingness-to-report depends in part upon the discretion of the workers. Hence, less severe injuries often go unreported. The authors suggested improvements to the current PERKESO database in order to increase its utility, especially for prevention purposes. Reporting of all injuries (including those less-severe ones) should be made mandatory by PERKESO. Some of the classifications within PERKESO database, such as type of injury, need to be revised to avoid misclassification. A national injury surveillance system (specifically tailored for occupational health surveillance) should be developed to include all categories of employees.

Al-Husuny *et al.* studied work-related hand injuries (WRHIs) in Hospital Universiti Kebangsaan Malaysia (HUKM).⁹ The authors found that 24.9% of industrial accidents were WRHIs and 30% of all occupational accidents seen in the emergency department involved the hands. This study found a significant association between the severity of WRHIs and the locations of injury, mechanisms of injury, sources of injury and sectors of industry. WRHIs occurred most commonly in industries such as manufacturing, construction and food preparation. Seventy percent of hand injuries were caused by operating machines. Machine operators were found to be 26 times more prone to experience severe WRHIs. Fifty four percent of workers with WRHIs were from metal machinery industry. Employees in this industry had an 8 fold higher risk of sustaining severe WRHIs.

Abdullah *et al.* also conducted a study on 57 workers admitted to HUKM for acute hand injuries sustained at work.¹⁰ The vast majority (93%) of workers were male. About half (48%) of the workers were between 25 to 35 years old. The right hand was more often affected compared to the left. Most of the injuries involved the fingers. More injuries occurred on the weekends. Lacerations were the most common injury followed by fractures and crush injuries.

Anuar *et al.* conducted a 5-year survey on laboratory-acquired injuries in 3 medical laboratories (Hospital Kuala Lumpur (HKL), HUKM, and Pusat Perubatan University Malaya (PPUM)).¹¹ The average annual incidence was 2.05 per 100 full-time equivalent (FTE) employees which is lower than that in the United States (2.1 per 100 FTE, BLS 2006). The annual incidence rate in each individual medical laboratory is 2.04 per 100 FTE (HKL), 2.07 per 100 FTE (HUKM) and 2.04 per 100 FTE (PPUM) employees, respectively. From year 2001 to year 2005, the most common injuries were cuts by sharp objects (24 cases, 25.3%) followed by exposure to biohazards and chemical substances (18 cases, 19.9%), needle-prick injuries (16.8%), fire (8.4%), falls/slips (6.3%), gas leak (1 case) and locked in a cold room (1 case). There was an increasing

annual incidence from the year 2001 to year 2004; however, it decreased in the year 2005. The authors attributed this reduction to the fact that these laboratories were seeking accreditation with the relevant agencies and had hence improved their safety practices. This study helped to identify those areas in laboratory safety that needed improvement.

Dayang *et al.* analyzed accidents in the construction industry which were reported to the Department of Occupational Safety and Health (DOSH), Social Security Organization (SOCSO) as well as the Construction Industry Development Board (CIDB).¹² The authors remarked that the construction sector was a highly hazardous industry and that SOCSO recorded an increasing incidence of injuries which had resulted in permanent disabilities and fatalities from year the 1996 till 2008. The Department of Occupational Safety and Health (DOSH) under the Ministry of Human Resources recorded an increase in the number of accidents within the construction industry, with severe and fatal accidents occurring every month in the years 2007 and 2008 (17 cases in the year 2007 and 12 cases in the year 2008).

Htay *et al.* conducted a cross-sectional study on the profile of injuries in villages within the Jasin district of Melaka.¹³ The study showed that 56% of villagers reported sustaining injuries in the one-year period. Home injuries were the most common (60.2%), followed by road traffic injuries and occupational injuries. Falls were the most common type of injuries at home and mostly occurred in the evening. Road injuries most commonly occurred in the evening and at night. The extremities were the most-severely injured. Most of the injured villagers preferred to seek treatment from the government healthcare facilities.

Jegatheswaran *et al.* studied the occupational accidents among migrant contract workers in the furniture industry.¹⁴ Migrant contract workers were found to be more productive and had a lower incidence of occupational injuries than their local counterparts. The authors attributed this to a better compliance with occupational safety and health practices.

Zainal *et al.* conducted a case-control study on occupational accidents among the Royal Malaysian Navy personnel in Lumut.¹⁵ This study showed that the Malays had the lowest incidence of injuries compared to personnel of other races.

Prevention and Management

Adinegara *et al.* conducted a study on fatal and non-fatal occupational injuries and found a decreasing annual incidence of occupational injuries.^{7,8} The authors attributed this to a more organized workplace, and an increased attention to safety and health practices in the workplace. The government had allocated additional resources under the 9th Malaysia plan (2006 – 2010) for the enforcement of OSHA 1994. However, the mechanisms to ensure universal adherence to this regulation are lacking.

Ahmadon *et al.* published a review on “Occupational Safety and Health Management Systems (OSHMS)”.¹⁶ They concluded that a better understanding of OSHMS helps in its application and enforcement of legislations.

Hassan *et al.* studied the influence of management practices on safety culture and found that organizations with good safety practices had fewer occupational injuries.¹⁷ Such organizations benefited through a reduced loss-of-work hours and amount of compensations offered for accidents. Employees are hence more motivated and this will increase the productivity of the organization. This study also revealed that the attitude of individual employees influenced the incidence of occupational injuries. The authors suggested that further studies on the relationships between workers’ safety awareness, risk perceptions, participation in safety committees and the incidence of workplace injuries.

Dayang *et al.* suggested that it was the employer’s negligence that was responsible for the occurrence of accidents within the construction sector.¹⁸ The Construction Industry Development Board came up with a Master Plan for Occupational Safety and Health within the Construction Industry. The plan helps all stakeholders to strengthen their OSH activities. This master plan focuses on six areas as identified by the National OSH committee for the construction industry. These six areas are (i) Enforcement & Legislation, (ii) Education and Training, (iii) Promotions, (iv) Incentives & Disincentive, (v) Standards and Research & (vi) Development and Technology¹⁰. Similar plans need to be developed for other high-risk occupational areas.

Ali *et al.* found that only a third (33.6%) of workers received OSH training before or within a month of starting work.¹⁹ This study also found that only 38.9% of workers that felt that they needed PPE were given so by their employers. The authors suggested further research to identify the reasons for the lack of risk reduction practices in the workplace.

Lugah *et al.* conducted a survey to assess OSH knowledge among healthcare professionals²⁰. About a third (34.2%) of respondents had a good knowledge of OSH. Doctors had a better knowledge on OSH compared to other healthcare workers. Nurses and administrative staff had the poorest knowledge on OSH. Administrative officers usually represent employers within the OSH committee and this may lead to a less emphasis on OSH within the workplace. This survey also showed that healthcare workers were most knowledgeable about personal protective equipment (PPE) (mean score of 72.0 %) compared to other areas such as the general OSH (58%), legislations (57%), and occupational hazards (64%). The authors suggested for more training workshops to promote OSH knowledge.

Abdullah *et al.* made some recommendations to reduce occurrence of occupational hand injuries.¹⁰ The authors suggested for a proper working technique, a conducive working environment and wearing of protective gadgets. They suggested for a longer period of rest for workers since fatigue may reduce attention to safety practices.

Jegatheswaran *et al.* suggested improving workforce psychology to improve workers attitude towards OSH, and to reduce the rate of occupational accidents.¹⁴

Htay *et al.* had recommended environmental and behavioral modifications together with community participation at a district level to prevent injuries at home¹³.

Chan *et al.* reviewed the occupational rehabilitation services in Malaysia and Singapore.²¹

Efforts to rehabilitate injured workers are generally lacking in Malaysia. Publications on occupational rehabilitation are scarce. The authors suggested that the Ministry of Health (MOH) rather than the Ministry of Human Resources should be responsible for providing occupational rehabilitation services. MOH has more personnel and expertise to provide occupational rehabilitation services. However, the authors recommended that their clinical skills and knowledge needs to be enhanced. There should also be more awareness among employers and funding for provision of occupational rehabilitation services. A closer cooperation between various ministries and departments is needed to improve the delivery of occupational rehabilitation services.

Murad *et al.* conducted a study to assess the relationship between occupational competence (OC) and emotional health among injured workers participating in the Return To Work (RTW) programs.²² The results showed that injured workers had a significantly lower OC and a significantly higher NES (Negative Emotional States) especially in the off duty and re-entry phases. This study also showed that lower levels of OC were associated with higher levels of NES. The authors suggested that the RTW programs should focus more on OC and NES and not just on physical defects. The authors also suggested that psychologists and occupational therapists should be given a more active role in the RTW programs.

Rozali *et al.* reported a case study of decompression illness in a diver working for a private company.²³ He developed decompression illness when he ascended suddenly from a depth of 48 meters because his tank ran out of air. The authors recommended that all decompression illness should be notified. All divers should be registered with SOCSO.

SECTION 2: RELEVANCE OF FINDINGS FOR PRACTICE AND FUTURE RESEARCH DIRECTION

Malaysia is a developing nation undergoing rapid industrialization. OSH practices play an important role in improving organizational efficiency by reducing labour cost and loss-of-work hours due to injuries. They, therefore, have a significant impact on the national economy. Descriptive research helps in identifying the magnitude and impact of occupational injuries while analytical studies on practices of both workers and management helps to examine the causes of injuries with a view to develop preventive measures.

The National Institute for Occupational Safety and Health (NIOSH), United States has recommended an occupational research agenda encompassing the traditional public health model²⁴. This includes (a) injury surveillance to identify and prioritize the magnitude of the problem (b) analytic research to establish risk factors and causative mechanisms (c) identification of effective strategies or developing new strategies for prevention (d) effective intervention through widespread communication, enforcement and technology transfer and (e) evaluation of interventions.

Further research should also focus on safety practices and enforcement of OSHA in high-risk industries such as transportation, agriculture and construction. Pilot interventions should be implemented and evaluated for widespread implementation. Studies of hazards in the environment (including machinery and equipment) should be encouraged and preferably carried out by the concerned industries.

Standard operating procedures for the proper handling of industrial equipment should be evaluated for feasibility and compliance. The efficacy of standard safety practices such as rotation of workers in hazardous work areas should be evaluated.

In conclusion, research on occupational injury in Malaysia is generally lacking and needs to be strengthened. Future research should focus on high-risk industries (agriculture, construction and transportation), Future occupational management systems and the role of a safer design of the environment including equipment and machinery. The effectiveness of OSHA should be evaluated and measures to further implement it should be developed. Comparative research into the effectiveness of occupational safety practices in our country with other developed nations will be helpful.

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