SUPPLEMENT 6

HONG KONG MEDICAL JOURNAL 香港醫學雜誌 Volume 22 Number 6 December 2016 22(S6)

HONG KONG

Volume 22 Number 6 **December 2016**

The official publication of the
Hong Kong Academy of Medicine and
the Hong Kong Medical Association

MEDICAL JOURNAL
香港醫學雜誌

Health and Health Services Research Fund
Research Fund for the Control of Infectious Diseases

Research Dissemination Reports

衛生及醫護研究基金
控制傳染病研究基金

研究成果報告

Cancer
癌症

Cardiovascular Diseases
心血管疾病

Mental Health
心理健康

Neurology
神經病學

Physical Activity / Obesity
身體活動 / 肥胖

Supplement 6

ISSN 1024-2708

香港醫學專科學院出版社
HONG KONG ACADEMY OF MEDICINE PRESS

HONG KONG MEDICAL JOURNAL 香港醫學雜誌
Volume 22 Number 6 **December 2016**
SUPPLEMENT 6

Health and Health Services Research Fund
Research Fund for the Control of Infectious Diseases

Research Dissemination Reports

NEUROLOGY

PHYSICAL ACTIVITY / OBESITY

Editorial

Dissemination reports are concise informative reports of health-related research supported by funds administered by the Food and Health Bureau, for example, the *Health and Health Services Research Fund* and the *Research Fund for the Control of Infectious Diseases* (which was consolidated into the *Health and Medical Research Fund* in December 2011). In this edition, 10 dissemination reports of projects related to cancer, cardiovascular disease, mental health, neurology, and physical activity/obesity are presented. In particular, four projects are highlighted due to their potentially significant findings, impact on healthcare delivery and practice, and/or contribution to health policy formulation in Hong Kong.

In Hong Kong, breast cancer is the most common cancer and the third leading cause of cancer-related mortality among women. The rapid development of Hong Kong over the last 60 years is expected to be reflected in breast cancer incidence and mortality. Wong et al.[1] examined the incidence trend using population data and age-period cohort models. They forecast the future trends for the short- to medium-term based on the extrapolation of trends in earlier periods. They found that the increased risk in breast cancer incidence has continued, likely owing to ageing and cohort effects. However, breast cancer mortality has remained stable during the past three decades despite some increased projections in older women.

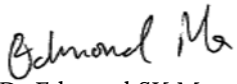
Cardiovascular diseases are the leading cause of death worldwide and are expected to increase over the next two decades, particularly in developing countries or migrant populations that undergo rapid economic development, such as Hong Kong. Understanding cardiovascular risk among migrants and migrant generations in Hong Kong may identify target groups for effective early disease prevention. Hui et al.[2] used data from a large population representative Hong Kong Chinese birth cohort to examine the role of migration in cardiovascular-related risk factors observed in adolescence. They found that early childhood migrants and children of migrant women had more cardiovascular disease–related risk factors in adolescence.

Expressed emotion refers to the amount of criticism, hostility, positive remarks, warmth and emotional over-involvement expressed in family relationships, particularly among relatives of a psychiatric patient. Of the five components, criticism, hostility, and emotional over-involvement are most predictive of patient's relapse and course of illness and are associated with patient's symptoms, compliance with medication, family burden, and functioning. Chien et al.[3] translated and validated the Level of Expressed Emotion scale in a large convenience sample of Chinese outpatients with severe mental illness in Hong Kong. The locally validated scale may be useful in evaluating the emotional climate and interpersonal relationships in families of mentally ill patients.

Dementia is characterised by cognitive decline and functional impairment in older people and is a growing problem in Hong Kong because of its ageing population. Minimising the detrimental effect of risk factors and optimising resilience factors may help prevent or postpone the onset of dementia and reduce functional impairment of older people as well as associated healthcare costs. Lee et al.[4] assessed the association of basic physical health and lifestyle factors with the development of significant cognitive impairment in community-living active Chinese older people in Hong Kong. They found that the 6-year incidence of significant cognitive impairment in the study population was 8.6%. Old age, female gender, and low educational level are risk factors for its development, while endurance exercises, stretching exercises, and mental activities are protective.

We hope you will enjoy this selection of research dissemination reports. Electronic copies of these dissemination reports and the corresponding full reports can be downloaded individually from the Research Fund Secretariat website (http://www.fhb.gov.hk/grants). Researchers interested in the funds administered by the Food and Health Bureau also may visit the website for detailed information about application procedures.

Supplement co-editors



Dr Edmond SK Ma
Consultant
(Research Office)
Food and Health Bureau

Dr Richard A. Collins
Scientific Review Director
(Research Office)
Food and Health Bureau

References

1. Wong IO, Schooling CM, Cowling BJ, Wong CN, Leung GM. Disease burden of breast cancer in Hong Kong: an exploration of trends for screening policy and resource allocation. Hong Kong Med J 2016;22(Suppl 6):S4-7.
2. Hui LL, Wong MY, Chung TW, Lee KK, CM Schooling. Migration status and cardiovascular disease risks in Hong Kong adolescents. Hong Kong Med J 2016;22(Suppl 6):S19-23.
3. Chien WT, Chan ZC, Chan SW, Yip LK, Ip G. Psychometric properties of a Chinese version of the Level of Expressed Emotion scale and expressed emotion of family members perceived by patients with severe mental illness. Hong Kong Med J 2016;22(Suppl 6):S28-34.
4. Lee AT, Chan WC, Chiu HF, et al. Physical health and lifestyle predictors for significant cognitive impairment in community-dwelling Chinese older adults in Hong Kong. Hong Kong Med J 2016;22(Suppl 6):S37-9.

Disease burden of breast cancer in Hong Kong: an exploration of trends for screening policy and resource allocation

IOL Wong *, CM Schooling, BJ Cowling, CN Wong, GM Leung

KEY MESSAGES

1. The increased risk in breast cancer incidence has continued, likely owing to ageing and cohort effects. Nonetheless, breast cancer mortality has remained stable during the past three decades despite some increased projections in older women.
2. Future research to investigate the underlying reasons for the increased projections for older women is warranted.
3. Strong birth cohort trends in breast cancer incidence and mortality are observed.
4. Some birth cohorts have a higher risk of developing breast cancer but a lower chance of dying from it. This can be explained by early detection and the availability of better treatment.
5. The lower risk for women in the 1910s birth cohorts may reflect possible dietary restriction at early ages in the 1910s and the 1920s.

Hong Kong Med J 2016;22(Suppl 6):S4-7
HHSRF project number: 10111031

IOL Wong, CM Schooling, BJ Cowling, CN Wong, GM Leung

School of Public Health, LKS Faculty of Medicine, The University of Hong Kong

* Principal applicant and corresponding author: iolwong@hku.hk

Introduction

Breast cancer is the most common malignancy and the leading cause of cancer-related death in women, accounting for 10% of new malignancies worldwide annually, and ~22% of all female malignancies.[1] In Hong Kong, breast cancer is the most common cancer and the third leading cause of cancer-related mortality among women, with an age-standardised incidence and mortality of 61.0 and 9.1 per 100 000 in 2011, respectively.[2] The incidence in Hong Kong is rising and exceeding all other East Asian populations except Singapore.[1] Nonetheless, the death rate in Hong Kong has been stable over the past three decades.[2]

Age-period-cohort (APC) models have been used to examine trends in the incidence and mortality over time as well as different biological and environmental causes of cancer.[3] Hong Kong has a history of rapid economic transitions over the past 60 years. Within two to three generations, Hong Kong has transformed from a third-world economy to a major financial centre. Socio-economic development is often followed by improved living standard and clinical interventions that are expected to affect the incidence and mortality of breast cancer. The economic and socio-cultural context of Hong Kong serves as a natural testing ground to examine how contextual history is related to the disease burden associated with breast cancer in a Chinese population.

During the 1990s, progress in early detection and treatment of breast cancer resulted in a decreasing mortality in Caucasian populations. Disparities in the disease incidence and mortality by age group were also observed. It is not known whether the same is found in non-Caucasian populations, such as the Chinese population in Hong Kong. This can be determined by investigation of the trend and projection for breast cancer mortality in Hong Kong.

This study aimed to (1) examine the incidence trend using recently available population data and the APC model; (2) estimate the relative effects of age at diagnosis, period of diagnosis, and birth cohort on trends in breast cancer incidence and mortality using the APC model with reference to the life course theory; and (3) forecast the future trends for the short- to medium-term based on the extrapolation of trends in earlier periods.

Methods

This study was conducted from October 2012 to September 2013 and has been published elsewhere.[4] According to the International Classification of Diseases (ICD) codes of ICD-8 174, ICD-9 174, ICD-10 C50, and C50.0-C50.9, age-specific breast cancer incidence, mortality, and mid-year population figures from 1976 to 2010 were retrieved from the Hong Kong Cancer Registry, Hong Kong Death Registry, and the Census and Statistics Department, respectively. New cases and all deaths associated with breast cancer during the period were included.

Given that breast cancer incidence/mortality was not common for very young age groups, fourteen 5-year age groups from 20-24 to ≥85 years, and seven 5-year periods from 1976-1980 to 2006-2010 were classified.

The age-adjusted incidence and mortality trends (per 100 000 women) in Hong Kong were calculated by a direct-standardisation method, according to the World Standard Population in 2000. By using Joinpoint regression analysis, the trends of breast cancer incidence and mortality from 1976 to 2010 were characterised using segmented annual percentage changes and the overall percentage change (OPC).

APC regression analysis and fitted Poisson regression models on the chronological age, calendar period, and birth cohort effects were conducted. Bayesian inference was applied to estimate the model parameters, and the fitted model was used to project future incidence/mortality in three 5-year periods up to 2025. The parameter estimates and the derived rates were summarised in terms of posterior means and 95% credible intervals. The model goodness-of-fit was measured by the posterior mean deviance D. The resulting models were used to project age-standardised breast cancer incidence and mortality in the short to medium term (until 2021-25). The uncertainty associated with our projections was quantified using 95% projection intervals. All analyses were implemented using Joinpoint 4.0.1, R version 2.10.1 and WinBUGS version 1.4.

Results

Temporal patterns in age-standardised incidence and mortality during 1976-2010 and projections for 2011-2025

The changes in breast cancer incidence or mortality were quantified in terms of segmented annual percentage changes and OPCs (Fig 1). The fourth period centred at 1993 was marked by a joinpoint at which the slope changed significantly for both the incidence and mortality trends. The incidence increased significantly by 1.24% per year until the 5-year period centred at 1993, and then increased further by 2.14% per year. In contrast, mortality increased by 0.35% per year until 1993, and then decreased significantly by 0.39% per year after 1993.

The age-standardised annual incidence rose by a mean of 1.69% per year in the three decades between 1976 and 2010 ($OPC_{incidence,1976-2010}$=1.69). The age-standardised breast cancer incidence was predicted to increase from 56.7 in 2011-15 to 62.5 in 2021-25 per 100 000 women. In contrast, age-standardised annual mortality decreased by a mean of 0.03% per year between 1976 and 2010 ($OPC_{mortality,1976-2010}$=0.03). The rate was projected to decline from 9.3 in 2011-2015 to 8.6 in 2021-2025 per 100 000 women.

Age-period-cohort analyses of breast cancer incidence and mortality trends

The estimated parameter values of the age, period, and cohort components are shown in Fig 2. Due to the identifiability problem of the APC models, where the effects of the three components are linearly dependent, only second-order changes (ie changes in slopes or inflection points) were interpretable. Three inflection points for mortality and incidence trends were readily identified, while there were negligible second-order changes in period effects. In other words, cohort effects were significant in both incidence and mortality trends from 1976 to 2010, but period effects were not significant. With respect to the inflection points for the two birth cohort curves, the first two inflection points (1910 and 1930) coincided and the third inflection points for mortality and incidence birth cohort curves were different (1950 and 1960, respectively).

Deviance information criteria for different combinations of age, period, and cohort effects were also estimated (data not shown). The full APC model provided the best fit with substantially smaller values of deviance information criteria compared with the other partial models.

Trends in incidence and mortality by age group

Incidence trend was projected to increase into the near future for women older than 55 years. Mortality

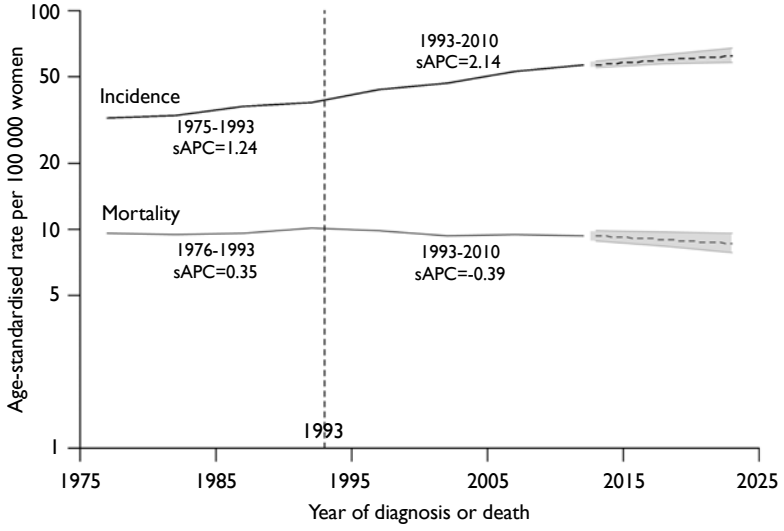


FIG 1. Annual age-standardised female breast cancer incidence and mortality in Hong Kong from 1976 to 2010 and projected incidence and mortality (dotted lines) to 2025 with 95% credible intervals (grey area). The segmented annual percentage change (sAPC) was significantly different from zero (P<0.05), from which the period centred at 1993 (vertical dotted line) was marked by a joinpoint at which the slope changed significantly in both the incidence and mortality trends.

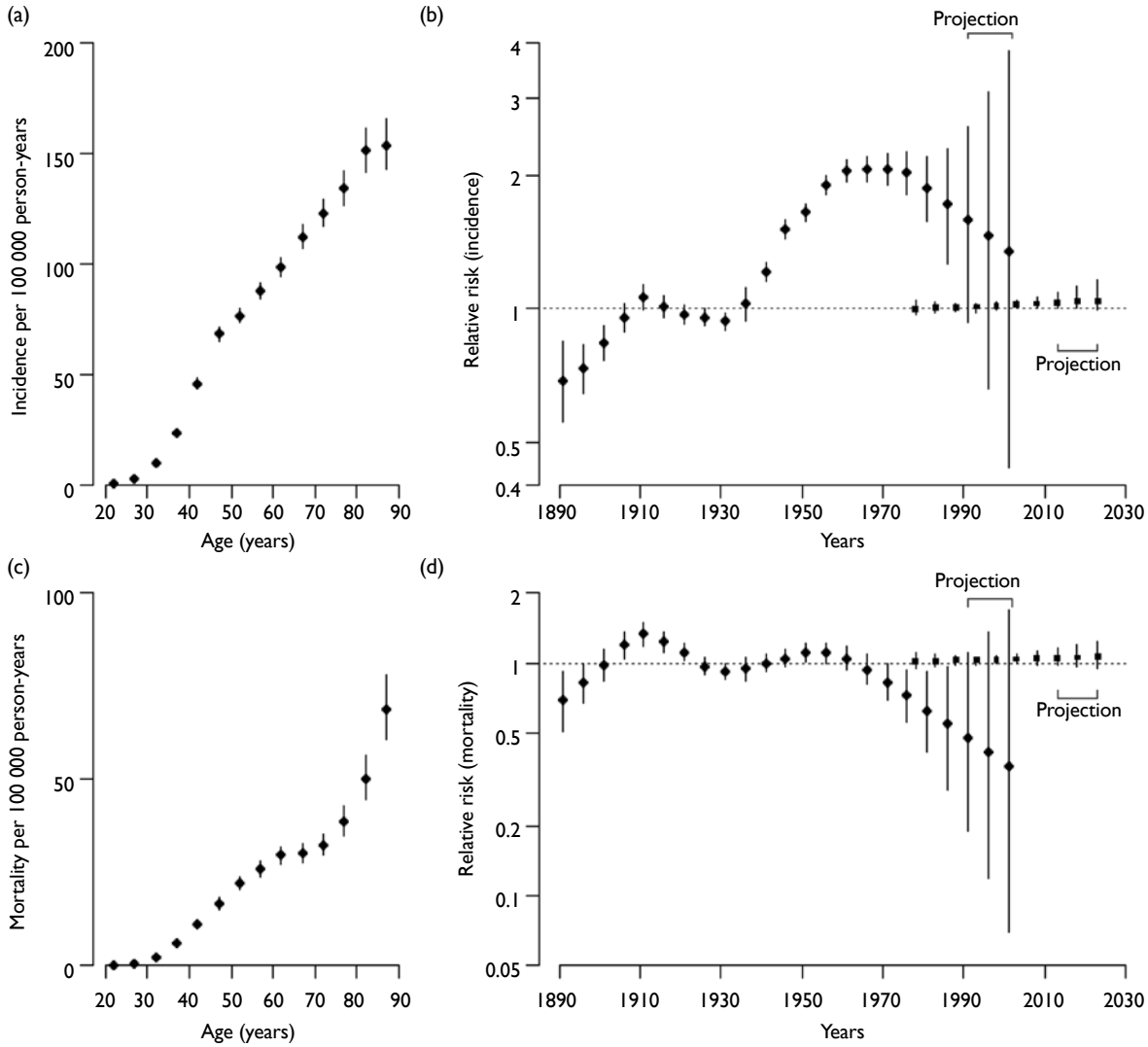


FIG 2. Parameter estimates of age, period, and cohort effects from two age-period-cohort models for female incidence and mortality trends related to breast cancer (deviance information criteria being 916.60 for incidence model and 737.44 for mortality model). Estimated age-specific annual female (a) incidence and (c) mortality related to breast cancer in 5-year age groups in Hong Kong with 95% credible intervals. Estimated relative risks for 10-year birth cohort (beginning from 1889) and 5-year period effects (beginning from 1976) associated with (b) incidence cases and (d) deaths with 95% credible intervals, including projected cohort effects for birth cohorts centred on the years 1993, 1998, and 2003 and projected period effects for periods centred on the years 2013, 2018, and 2023.

trend was projected to decline in the near future for women aged <65 years but increase for those aged ≥65 years.

Discussion

Our findings predict that breast cancer incidence will continue to increase at 0.65% per year, whereas mortality will decrease at 0.56% per year between 2010 and 2025. Cumulatively, this represents a projected increase of 10.2% in incidence and a decrease of 7.5% in mortality. The incidence trends seem to have been driven mainly by ageing and birth cohort effects (ie the intergenerational effects were mainly driven by the post baby boomers), and there are no clear non-linear changes in trend by time-period effect. In contrast, the mortality trend has been relatively stable compared with the increasing incidence trend over the past three decades. The temporal trends in mortality might be explained by an improvement in survival due to better treatment for breast cancer and better responses to newly developed therapy such as paclitaxel use in the 1990s, and adjuvant hormonal and targeted immunotherapy in the 2000s.

Strong birth cohort trends were observed in breast cancer incidence and mortality, with inflection points around birth cohorts at 1910, 1930,

and 1960, and at 1910, 1930, and 1950, respectively. These effects could have been brought about by key historical events that altered the breast cancer risk factors at a population level.

Among the earliest birth cohorts, there was a deceleration in disease risk in incidence and mortality, especially in the 1910s birth cohorts. This trend coincided with the collapse of the Qing dynasty and a subsequent fall in living standards. The lower risk for these women might reflect possible dietary restriction at early ages in the first two decades after the revolution in 1911. Moreover, the increase in disease risk and mortality for the birth cohorts during the 1930s period coincided with the first cohort of women who migrated from China to Hong Kong. The mortality trend might reflect changes in incidence and poorer long-term survival in the period before World War II. The deceleration at around 1960 in birth cohort effects on the risk of developing the disease coincided with the last cohorts of women who had lived some years of their puberty in China. This generation of Hong Kong Chinese women grew up in a rapidly growing economy. Interestingly, the birth cohort around 1960s was at higher risk of developing the disease but at lower risk of death than previous generations. This might be explained by early detection and the availability of better treatment.

We projected a reduction in age-specific mortality for women aged ≤65 years, and a rising trend in mortality among women older than 65 years during 2010-25. In comparison with western countries that have had major socioeconomic transition in the more distant past, a reduction in mortality trends is observed in the younger age group (<50 years) in Hong Kong, regardless of the national screening level in young women.[5] This relatively larger reduction may reflect more effective cancer treatment and better response to treatment.[5] These same reasons could apply to the Hong Kong context. It is nonetheless unclear why mortality increased for much older women in Hong Kong. This could be attributed to a combination of less frequent diagnostic activity, less intensive treatment, and more frequent diagnosis of cancer at an advanced stage.[5] Increased mortality projection in older women suggests a need to investigate the underlying reasons and extend access to better treatment and medical technologies for all segments of the population whenever applicable.

There were limitations to the study. APC analyses are descriptive in nature. We can only speculate the aetiology of the changes observed. Nonetheless, our analyses can generate hypotheses about the relationship between cancer disease risk and potential risk factors. The reliability of APC analyses depends on the quality of the incidence and mortality data. The Hong Kong Cancer Registry is the most carefully validated source of data. Quality indicators suggest that our data quality matches international standards.

Acknowledgements

This study was supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (#10111031). We thank the Census and Statistics Department of the Hong Kong SAR Government for their support and for facilitating mortality data access, although they have no role in the design, analysis, interpretation or decision to submit for publication.

Results of this study have been published in: Wong IO, Schooling CM, Cowling BJ, Leung GM. Breast cancer incidence and mortality in a transitioning Chinese population: current and future trends. Br J Cancer 2015;112:167-70.

References

1. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002. Cancer incidence, mortality and prevalence worldwide. IARC CancerBase No. 5, version 2.0. Lyon: IARC Press; 2004.
2. Hong Kong Cancer Registry. Hong Kong Cancer Registry. 2013.
3. Holford TR. Understanding the effects of age, period, and cohort on incidence and mortality rates. Annu Rev Public Health 1991;12:425-57.
4. Wong IO, Schooling CM, Cowling BJ, Leung GM. Breast cancer incidence and mortality in a transitioning Chinese population: current and future trends. Br J Cancer 2015;112:167-70.
5. Autier P, Boniol M, LaVecchia C, et al. Disparities in breast cancer mortality trends between 30 European countries: restrospective trend analysis of WHO mortality database. BMJ 2010;341:c3620.

Perceptions of cancer risk and self-care practices: comparison of groups at different risk for cancers

R Fielding *, WWT Lam, QY Liao, CL Lai, JWH Tsang, D Ip, MF Yuen

KEY MESSAGES

1. Groups with predisposing risk factors generally perceived themselves to have a higher susceptibility to the cancers to which they were vulnerable, with the exception of female passive smokers.
2. Nonetheless, in predisposed individuals, their perceived higher susceptibility to cancer remains markedly lower than their actual risk derived from current risk projection. Over 60% of smokers, hepatitis B (HBsAg) carriers, and female relatives of breast cancer patients underestimated their risk of cancer relative to that derived from current risk projections.
3. HBsAg carriers and female relatives of breast cancer patients reported a higher optimism score compared with other groups and lived a healthier lifestyle, whereas smokers were more likely to be regular drinkers and consumed less fruit and vegetables.
4. Optimism was positively associated with adopting measures to maintain health

Hong Kong Med J 2016;22(Suppl 6):S8-12
HHSRF project number: 08090791

[1] R Fielding, [1] WWT Lam, [1] QY Liao, [2] CL Lai, [3] JWH Tsang, [1] D Ip, [2] MF Yuen

[1] *School of Public Health, The University of Hong Kong*
[2] *Department of Medicine, University of Hong Kong Medical Centre, Queen Mary Hospital*
[3] *Department of Clinical Oncology, Queen Mary Hospital*

* Principal applicant and corresponding author: fielding@hku.hk

Introduction

Individuals with cancer-related risk factors are more vulnerable to certain types of cancer compared with those without such factors. Smokers have 20-25 times excess risk of lung cancer compared with never smokers.[1] Individuals who carry the BRCA I genetic mutation have 60-85% lifetime risk of developing breast cancer.[2] Chronic hepatitis B (HBsAg) infection increases the risk of hepatocellular cancer by 223 times.[3] However, people generally tend to underestimate their actual risk (optimistic bias); this may lead to failure to take necessary preventive action. Unmodifiable risks (genetic factors and acquired viral infection) are perceived to be a greater threat than modifiable risks (smoking and meat consumption). Smoking and breast cancer genetic risk are the most prominent cancer risks addressed in contemporary media. This should amplify their perceived riskiness relative to the cancer risk associated with viral infection. Perceived risk affects adoption of protective actions; its effect on behavioural change can be mediated or moderated by cognitive factors such as optimism, worry, and perceived self-efficacy.

This study compared risk perception of cancer between groups with different predisposing factors and its association with cognitive factors (optimism, perceived self-efficacy and worry about cancer) and lifestyle practices.

Methods

This multi-group cross-sectional study was conducted from January 2011 to December 2013 and was approved by the HKU/HIWC institutional review board. Five groups with different predisposing risks for a particular (target) cancer were recruited.

(1) Female first-degree relatives of breast cancer patients (BC-relatives): the relative was diagnosed with breast cancer before age 50 years but not known to be a BRCA polymorphism carrier. Eligible subjects were identified through eligible breast cancer patients who attended for follow-up at local breast centres. All eligible subjects were invited to complete a face-to-face interview.

(2) HBsAg carriers: asymptomatic patients recruited from local specialist clinics. Eligible subjects were referred by the clinic professionals and then approached by the project assistant for face-to-face interview.

(3) Smokers: asymptomatic and currently healthy adult smokers.

(4) Passive smokers: non-smoking adults living with a current smoker.

(5) Healthy adults: asymptomatic and currently healthy adults without the above predisposing factors (a family history of breast cancer, active smoking, living with a smoker, and HBsAg positive).

Smokers, passive smokers, and healthy adults were identified using randomly generated landline

numbers. For selected households, the person of first contact was asked whether any adult smokers were living in the household. If yes, one adult smoker and one adult non-smoker within the household were invited to participate. Otherwise, one adult whose birthday was closest to the survey date was invited.

Similar questionnaires were used for data collection for the five groups. Major outcome measures included:

(1) Perceived cancer risk: respondents were asked about their perceived absolute susceptibility and susceptibility relative to a general person of the same age and gender to each of the six common cancers in Hong Kong (ie breast, oesophageal, lung, liver, colorectal, and nasopharyngeal cancer) over the next 5 years. Scores ranged from 0 (very low) to 10 (very high). Respondents were also asked to estimate the prevalence of these cancers in Hong Kong on a scale of 0 (rarest) to 10 (very common). Respondents were asked to indicate how modifiable different types of cancer risk (genetic, acquired [viral], self-exposure [smoking, meat consumption]) and involuntary exposure (roadside air pollution, second-hand smoking) were on a scale of 0 (fixed, unmodifiable) to 10 (completely modifiable).

(2) Cognitive measures: these measured optimism, cancer-related worry, and perceived self-efficacy. Optimism was assessed using the validated Chinese Life Orientation Test – Revised. Perceived self-efficacy was assessed using the general self-efficacy scale validated in the Chinese population. Cancer-related worry was assessed using the Lerman Breast Cancer Worry Scale for worry about breast cancer for BC-relatives, which was adapted to also measure worry about lung cancer for smokers and passive smokers, and worry about liver cancer for HBsAg carriers.

(3) Lifestyle health practices: respondents' smoking and alcohol consumption behaviours, physical activity, and dietary habits were recorded using a standardised questionnaire. An open-ended question was also included to collect data on any other activities or supplements used by the respondents to improve or maintain their health.

Finally, respondents were asked about their health history, family history of cancer, and socio-demographics.

For data analysis, the actual risk of breast cancer among female respondents was assessed, as was hepatocellular cancer risk among HBsAg carriers and lung cancer risk among smokers and passive smokers, using best available risk prediction algorithms for those cancers. Perceived cancer risk score was converted into a 0-100% scale and categorised as <40% (low risk), 40-60% (moderate risk), or >60 (high risk). Bias in risk perception was the difference between respondents' actual and perceived relative risk: 'realistic' if actual and perceived relative risk was consistent, 'optimistic' if perceived risk was lower than actual risk, and 'pessimistic' if perceived risk was higher than actual risk. Respondents' perceived risk by type of cancer, optimism, perceived self-efficacy, and cancer worry were compared across groups stratified by gender, using the Kruskal-Wallis test for multiple-group comparison or Mann-Whitney *U* test with Bonferroni correction to adjust the type I error for pairwise comparison. Chi-square test was used to test the distribution of categorical variables between groups. Logistic regression was used to examine factors associated with healthy lifestyle practices.

Results

A total of 62 BC-relatives, 150 HBsAg carriers, 160 healthy adults, 151 smokers, and 153 passive smokers were recruited. Seven female respondents from the healthy group met the criteria of BC-relatives and were re-allocated. Seven respondents who were diagnosed with cancer were excluded. Thus, 69 BC-relatives, 150 HBsAg carriers, 149 healthy adults, 150 smokers, and 152 passive smokers were analysed. Generally, most smokers (72.7%) were males while most passive smokers (79.6%) were females. The HBsAg carriers were relatively younger (χ^2=39.03, d_f=8, P<0.001) and more likely to be single (χ^2=17.22, d_f=4, P=0.002). Smokers were more likely to have lower educational achievement (χ^2=16.96, d_f=8, P=0.030). Family income across the five groups was comparable.

Compared with healthy adults' perceived personal susceptibility to a particular cancer, BC-relatives perceived significantly higher personal susceptibility to breast cancer, as did smokers to lung cancer and nasopharyngeal cancer, and HBsAg carriers to liver cancer (Table 1). Male (but not female) passive smokers perceived marginally higher susceptibility to lung cancer (Table 1). HBsAg carriers perceived liver cancer to be more common in Hong Kong than did healthy adults, whereas male (but not female) passive smokers perceived lung cancer and nasopharyngeal cancer to be more common (Table 1). Generally, smoking was perceived to be the most-modifiable risk factor by all groups, except for male smokers, whereas genetic factors were perceived to be the least-modifiable risk factor (Table 1).

There was positive association between perceived personal susceptibility to and perceived prevalence of (1) lung cancer among smokers (χ^2=28.31, d_f=4, P<0.001), (2) liver cancer among HBsAg carriers (χ^2=11.94, d_f=2, P=0.03), and (3) breast cancer among BC-relatives (χ^2=8.63, d_f=2, P=0.013).

The Figure shows the prevalence of risk perception bias across groups for different cancers. Compared with the actual relative risk, over 60% of smokers, HBsAg carriers, and female relatives, and

TABLE. I Comparison of perceived risks by type and cognitive factors across groups

Perceived cancer risk	Healthy adults (n=149)		Smokers (n=150)		Passive smokers (n=152)		Hepatitis B carriers (n=150)		First-degree relatives of breast cancer patients (n=69)	P value for females across groups	P value for males across groups
	Female	Male	Female	Male	Female	Male	Female	Male	Female		
Perceived absolute susceptibility (score, 0-10)											
Breast cancer	3.14	-	3.49	-	2.82	-	2.94	-	4.54‡	<0.001	-
Oesophageal cancer	2.53	1.75	2.95	2.77	2.20	2.33	2.07	1.95	2.47	0.480	0.156
Lung cancer	2.33	2.23	5.22‡	4.48‡	2.99	3.63*	2.53	2.11	2.52	<0.001	<0.001
Liver cancer	2.66	2.35	3.80	3.25	2.33	2.67	4.52‡	4.13‡	2.67	<0.001	0.002
Colon cancer	2.85	2.74	3.07	2.69	2.46	2.73	2.81	2.47	2.78	0.453	0.900
Nasopharyngeal cancer	2.26	2.17	4.27‡	4.08‡	2.56	3.20	2.14	2.35	2.54	0.002	<0.001
Perceived comparative susceptibility (score, 0-10)											
Breast cancer	2.89	-	3.78	-	2.61	-	2.78	-	4.72‡	<0.001	-
Oesophageal cancer	2.54	2.18	3.20	2.61	2.35	2.40	2.17	1.97	2.60	0.258	0.623
Lung cancer	2.46	2.52	4.54‡	4.02‡	3.05	3.47	2.50	2.22	2.87	<0.001	<0.001
Liver cancer	2.96	2.73	3.78	3.10	2.61	3.03	4.50‡	4.09‡	2.91	<0.001	0.027
Colon cancer	2.71	3.02	3.60	2.72	2.51	3.13	2.70	2.52	3.12	0.069	0.546
Nasopharyngeal cancer	2.42	2.46	4.39‡	3.56	2.47	3.40	2.23	2.42	2.68	0.001	0.020
Perceived cancer prevalence (score, 0-10)											
Breast cancer	6.46	-	6.95	-	6.63	-	6.29	-	7.32	0.105	-
Oesophageal cancer	4.57	4.21	4.64	4.37	4.37	4.41	4.80	4.24	4.40	0.610	0.902
Lung cancer	6.37	6.16	7.05	6.01	6.73	7.31‡	6.83	6.43	6.35	0.163	0.047
Liver cancer	5.97	5.81	6.70	5.45	6.15	6.52	7.42‡	6.75‡	6.28	<0.001	<0.001
Colon cancer	5.68	5.46	4.85	4.73	5.23	5.86	6.06	5.48	6.05	0.002	0.044
Nasopharyngeal cancer	5.78	5.33	6.02	5.49	5.48	6.83‡	5.60	5.60	5.88	0.785	0.014
Perceived modifiability of risk types (score, 0-10)											
Exposure to air pollution	4.59	4.45	4.47	4.54	3.64	4.26	3.33‡	3.08‡	3.88	0.086	0.010
Exposure to second-hand smoke	5.10	5.74	5.60	5.13	5.18	4.97	4.48	5.84	5.61	0.178	0.161
Smoking	7.12	7.66	6.57	5.31‡	7.29	7.16	8.16	7.69	7.49	0.132	<0.001
Viral infection	5.06	4.93	4.15	4.79	4.81	4.43	4.40	5.15	5.46	0.047	0.592
Genetic factors	3.19	4.05	3.59	3.95	3.64	2.65	2.94	2.80‡	3.41	0.553	0.023
Meat consumption	5.27	5.22	5.82	5.17	5.59	5.61	6.08	5.74	6.12	0.144	0.386
Cognitive factors (score, 1-4)											
Optimism	2.67	2.63	2.62	2.63	2.71	2.74	2.87‡	2.81‡	2.92‡	<0.001	0.050
Self-efficacy	2.75	2.80	2.82	2.84	2.68	2.93	2.65	2.69	2.71	0.625	0.120
Cancer-related worry†	-	-	1.80	1.90	1.74	1.57	1.89	1.86	1.89	0.297	0.083

* P=0.020 after Bonferroni correction to adjust the type I error

† By risk type: worry about breast cancer for first-degree relatives of breast cancer patients, worry about lung cancer for smokers and passive smokers, and worry about liver cancer for hepatitis B carriers

‡ P<0.01 compared with that of healthy adults using Mann-Whitney *U* test with Bonferroni correction to adjust the type I error

only 27.6% of the passive smokers demonstrated optimistic bias in estimating their risk to the relevant target cancer. Compared with these at-risk groups, only 15.1% of the healthy males and 22.1% of healthy females demonstrated optimistic bias in estimating risk to lung cancer and breast cancer, respectively. Compared with the healthy controls, active smokers (OR=20.35, 95% CI=9.69-42.73) were more likely

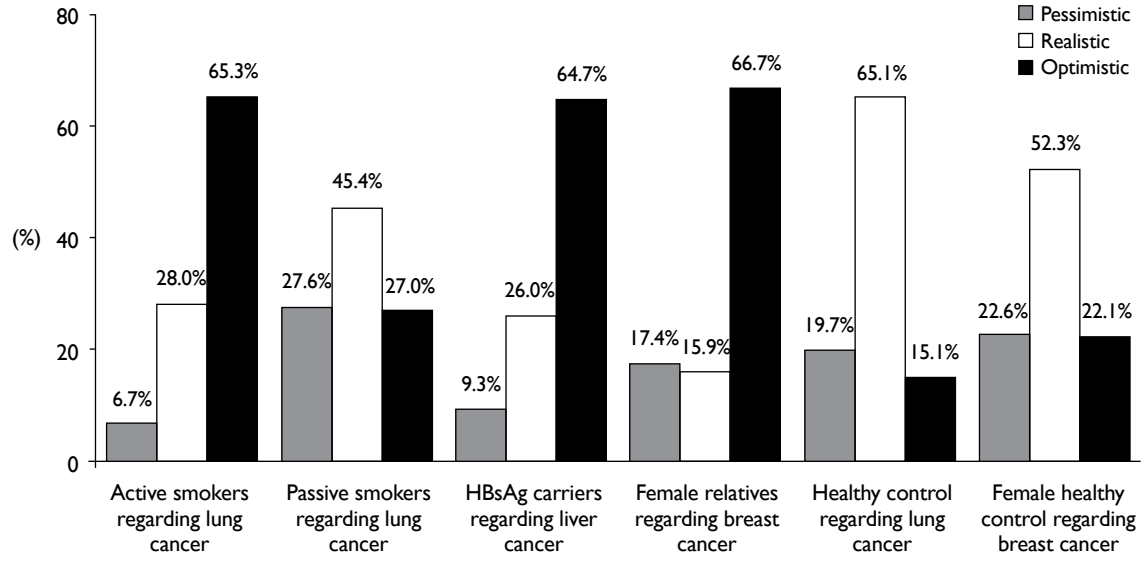


FIG. Bias in risk estimate among first-degree relatives of breast cancer patients, smokers, passive smokers, and hepatitis B (HBsAg) carriers

TABLE 2. Comparison of lifestyle practices across groups

Lifestyle practice	% adjusted for gender differences				
	Healthy adults (n=149)	Smokers (n=150)	Passive smokers (n=152)	Hepatitis B carriers (n=150)	First-degree relatives of breast cancer patients (n=69)
Alcohol consumption					
Never/occasional drinkers	59.2	37.7	56.5	54.4	54.4
Regular drinkers	40.8	62.3*	43.5	45.6	45.6
No. of current smokers	0	150	0	18	6
Physical activity					
Low level	22.8	22.0	19.1	25.2	34.4
Moderate level	42.3	44.7	51.3	42.0	39.3
High level	34.9	33.3	29.6	32.9	26.2
Sitting (hours per day)					
<8	60.2	66.5	66.9	63.3	67.9
≥8	31.8	33.5	33.1	35.7	32.1
Consumption of vegetable and fruit (serving per day)					
<4	62.1	73.5	66.4	50.7	55.6
≥4	37.9	26.5*	33.6	49.3*	44.4
Mean (female:male)	3.43:2.86	2.55:2.76	3.31:2.81	4.16:3.99	3.99
Consumption of red meat					
Never/seldom	16.2	17.3	15.1	23.4	26.1
≤3 times/week	35.8	26.7	26.3	37.9	42.0
≥4 times/week	48.0	56.0	58.6	38.6*	31.9
Any practices adopted to maintain health					
No	41.5	45.7	47.9	31.2	24.4
Yes	58.5	54.3	52.1	68.8	75.6*
Any methods adopted to reduce risk of cancer					
No	86.6	87.3	83.5	86.7	83.8
Yes	14.7	14.4	14.7	14.6	13.2

* P<0.05 compared with the healthy group

to have optimistic bias when estimating their risk to lung cancer after adjusting for gender, age, and educational attainment. Female relatives were more likely to have optimistic bias when estimating their risk to breast cancer (OR=17.95, 95% CI=6.50-49.56).

Compared with healthy adults' cognitive factors, HBsAg carriers and BC-relatives showed higher optimism, but smokers did not show higher optimism than non-smokers (Table 1). Generally, cancer-related worry was low among BC-relatives towards breast cancer, among HBsAg carriers towards liver cancer, and among smokers and passive smokers towards lung cancer (Table 1). There were no group differences in scores of perceived self-efficacy and cancer-related worry.

For lifestyle practices, compared with the healthy group, smokers were more likely to regularly drink alcohol and consume less vegetables and fruit. In contrast, HBsAg carriers consumed more vegetables and fruit per day but less red meat. HBsAg carriers and BC-relatives were also more likely to adopt measures to maintain health (Table 2).

Multivariate logistic regression was conducted to examine the association between perceived risk of cancer and cognitive factors and adoption of health maintenance practices, adjusting for age, gender, educational attainment, and risk group. There was no significant association between perceived risk of cancer and adoption of health maintenance; higher optimism was associated with being more likely to adopt measures to maintain health (OR=1.89, 95% CI=1.20-2.96).

Discussion

Female passive smokers who do not perceive higher personal susceptibility to lung cancer are an important target for health promotion/education. Previous review suggests that more support from partners, especially spouses, can facilitate and maintain smoking cessation.[4] Promoting passive smokers' perceived risk for lung cancer may help smokers to quit smoking. Even among groups who were well aware of their susceptibility to a particular cancer, optimistic bias remained quite prevalent. Although some argued that optimistic bias may be an adaptive process to reduce the anxiety that arises from the greater perceived susceptibility, other studies have suggested it may discourage protective behaviour.[5] Efforts should be made to promote the awareness of these susceptible groups about their objective risk in order to reduce optimistic bias and motivate necessary preventive behaviour. Our study also indicates that an optimistic personality may be associated with more adaptive coping. The role of optimism in coping with risk of cancer should be further explored. This may help develop interventions for high-risk groups, particularly smokers, to reduce their risky lifestyle behaviour.

Acknowledgement

This study was supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (#08090791).

References

1. Thun MJ, Henley SJ, Calle EE. Tobacco use and cancer: an epidemiologic perspective for geneticists. Oncogene 2002;21:7307-25.
2. van Golen K, Milliron K, Davies S, Merajver SD. BRCA-associated cancer risk: molecular biology and clinical practice. J Lab Clin Med 1999;134:11-8.
3. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. Lancet 1981;2:1129-33.
4. Park EW, Tudiver F, Schultz JK, Campbell T. Does enhancing partner support and interaction improve smoking cessation? A meta-analysis. Ann Fam Med 2004;2:170-4.
5. Branstrom R, Kristjansson S, Ullen H. Risk perception, optimistic bias, and readiness to change sun related behaviour. Eur J Public Health 2006;16:492-7.

Identification of pathogenic microRNAs in *Helicobacter pylori*-associated gastric cancer using a combined approach of animal study and clinical sample analysis

CH Cho *, J Yu, WKK Wu

KEY MESSAGES

1. miR-490-3p is progressively down-regulated in the development of gastric cancer.
2. The tumour suppressive role of miR-490-3p is established both *in vitro* and *in vivo*.
3. DNA methylation is involved in the down-regulation of miR-490-3p in gastric cancer.
4. SMARCD1 is a direct target of miR-490-3p.

Hong Kong Med J 2016;22(Suppl 6):S13-8
RFCID project number: 10090532

[1,2] **CH Cho**, [2] **J Yu**, [2] **WKK Wu**

The Chinese University of Hong Kong:
[1] *School of Biomedical Sciences*
[2] *Institute of Digestive Disease, Faculty of Medicine*

* Principal applicant and corresponding author: chcho@cuhk.edu.hk

Introduction

Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death worldwide. *Helicobacter pylori* is estimated to infect at least half of the world's human population. The attributable risk for both intestinal and diffuse types of gastric cancer conferred by *H pylori* is approximately 75%.[1] Only a few studies have addressed the role of miRNAs in inflammatory or pre-neoplastic states of gastric mucosa.[2,3]

In this study conducted from January 2011 to July 2013, we used a multi-level method with a combined approach of high-throughput miRNA array technique, an animal model of *H pylori* infection, clinical sample analysis, and functional assays and identified miR-490-3p as a tumour suppressor in *H pylori*-associated gastric cancer.

Methods

Mouse model of gastric carcinogenesis

To generate a mouse model of gastric carcinogenesis, C57BL/6 mice (6-8 weeks old) were inoculated with *H pylori* (SS1 strain) with or without N-methyl-N-nitrosourea (MNU). 240 p.p.m MNU was given in drinking water starting from about 7 weeks of age for a total of five cycles of a 1-week regimen followed by a 1-week pause. It was freshly prepared twice a week and light shielded. $1x10^9$ CFU/mL *H pylori* in 0.1 mL Brucella broth with 5% foetal bovine serum was inoculated on three alternate days, starting from about 18 weeks of age. Mice were divided into three groups: control, *H pylori*, and *H pylori* plus MNU and kept for 12 months before being sacrificed.

miRNA microarray and data analysis

miRNA microarray was performed as described previously.[4] Agilent mouse whole genome miRNA array (rel15) was used. The miRNA expression values were extracted. Hierarchical clustering and heat map was used to show the non-parametric grouping of the miRNAs.

Cell lines and clinical samples

HFE-145 was obtained from Dr Duane T Smoot of the Howard University. TMK1 was obtained from Dr Eiichi Tahara of the University of Hiroshima. AGS, BGC823, MKN-1, MNK-28, MNK-45, and YCC-10 were purchased from American Type Culture Collection (Manassas [VA], USA). Normal, intestinal metaplasia, gastric cancer tissue and paired gastric cancer and adjacent normal tissue were retrieved from the tissue bank at the Department of Anatomical and Cellular Pathology, Prince of Wales Hospital, Hong Kong.

miRNA quantification

Total RNA was isolated according to the protocol of TRIZOL reagent. Expression of mature miRNAs was determined using TaqMan MicroRNA Assays (Applied Biosystems, USA). U6 served as endogenous control.

Cell viability assay and cell cycle analysis

Cell viability was measured by MTT assay and followed the standard procedure. Cell cycle analysis was determined by propidium iodide staining using the standard procedure.

Cell migration and invasion assay

The migration and invasion assays were performed using sterilised transwell insert chambers according to standard procedures.

Colony formation and anchorage-independent cell growth

For colony formation analysis, 24 hours after transfection, 10^3 viable cells were placed in six-well plates and maintained in complete medium for 2 weeks. Colonies were fixed with methanol and stained with 0.1% crystal violet. Anchorage-independent growth assays were performed in six-well plates by suspending 10^3 transfected cells per well in 0.3% low melting temperature agarose (Sigma) on a 0.5% agarose base layer, both of which contained growth medium. Two weeks later, colonies were visualised by staining with 0.1% crystal violet.

Western blot

Western blot was carried out following standard protocols.

Construction of lenti-miR-490-3p

miR-490-3p precursor sequences were amplified using the following primers: sense 5'-ccggTCAACCTGGAGGACTCCATGCTGctcgag CAGCATGGAGTCCTCCAGGTTGtttttg-3' and antisense 5'-aattcaaaaaCAACCTGGAGGACTCC-A T G C T G c t c g a g C A G C A T G G A G TCCTCCAGGTTGA-3' and cloned into the pLKO.1-puro vector. pLKO.1-puro vector served as control. Virus packaging was performed in HEK 293T cells co-transfected with pLKO-miR-490-3p or pLKO-ctrl with pCMV-dR8.2 dvpr Vector and pCMV-VSVG Vector using Lipofectamine 2000 (Invitrogen). Viruses were harvested 48 hours after transfection, and viral titre was determined

Animal experiment

TMK-1 cells were infected with lenti-miR-490-3p or control in the presence of 10 μg/mL Polybrene (Millipore). After 48 hours, 2×10^6 cells in 50 μL PBS were injected subcutaneously into the dorsal region of 6-week-old male BALB/c nu/nu mice (n=6 for each group). Tumour volume was measured every 10 days. At the end of the experiment, mice were sacrificed and the tumours excised and weighed.

Luciferase reporter assay

The SMARCD1 3'UTR or the miR-490-3p binding site deleted SMARCD1 3'UTR were subcloned in the pMIR-REPORT™ reporter (Invitrogen). 200 ng of the pMIR reporter together with 1 ng of the pRenilla reporter (Promega) were co-transfected into the cells by lipofectamine 2000 (Invitrogen) according to standard protocols. After 48 hours of incubation, the transfected cells were re-transfected with miR-490-3p mimics or miRNA control and incubated for 3 days. The activity of the firefly luciferase and Renilla luciferase was measured using the Dual-Luciferase Reporter Assay System (Promega)

DNA methylation analysis

Genomic DNA was subject to bisulfite treatment using the EZ DNA Methylation Kit (Zymo Research, Irvine, CA) according to the manufacturer's protocol and stored at -80°C. Bisulfite treated DNA was used as the template in methylation-specific-PCR using primers specific to methylated or unmethylated miR-490-3p promoter.[5]

Statistical analysis

All data were expressed as mean±standard deviation from triplicate experiments. Analysis of variance (ANOVA) was used, followed by the Tukey's t-test or Pearson correlation analysis. A P value of <0.05 was considered statistically significant.

Results

H pylori inoculation induced gastritis, intestinal metaplasia and gastric cancer in mice

The histology of the mouse tissue samples was examined by two pathologists blinded to the treatment group. Four of five mice in the control group had normal histology and the remaining one showed very weak inflammation. For the *H pylori*-inoculated group, three of seven mice exhibited moderate-to-severe inflammation and the tissues were used for miRNA array. In the MNU-plus-*H pylori* group, four mice developed intestinal metaplasia, four developed gastric cancer, and one developed dysplasia.

MicroRNA array analysis and real-time PCR validation

mmu-miR-1, mmu-miR-133a, mmu-miR-133a*, mmu-miR-133b, mmu-miR-203, mmu-miR-205, and mmu-miR-490-3p showed progressive down-regulation in the inflammation–intestinal metaplasia–adenocarcinoma sequence (Fig 1a). Hierarchical clustering (Fig 1b) showed that the expression pattern of miRNAs from the control group and *H pylori* group were the most similar and they were separated first with MNU+Hp (intestinal metaplasia) group and then with MNU+Hp (cancer), suggesting our model correctly depicted gastric carcinogenesis. Real-time PCR validation revealed gradual down-regulation from inflammation to intestinal metaplasia to cancer for miR-133a, miR-133b, miR-203, and miR-490-3p (Fig 1c). This

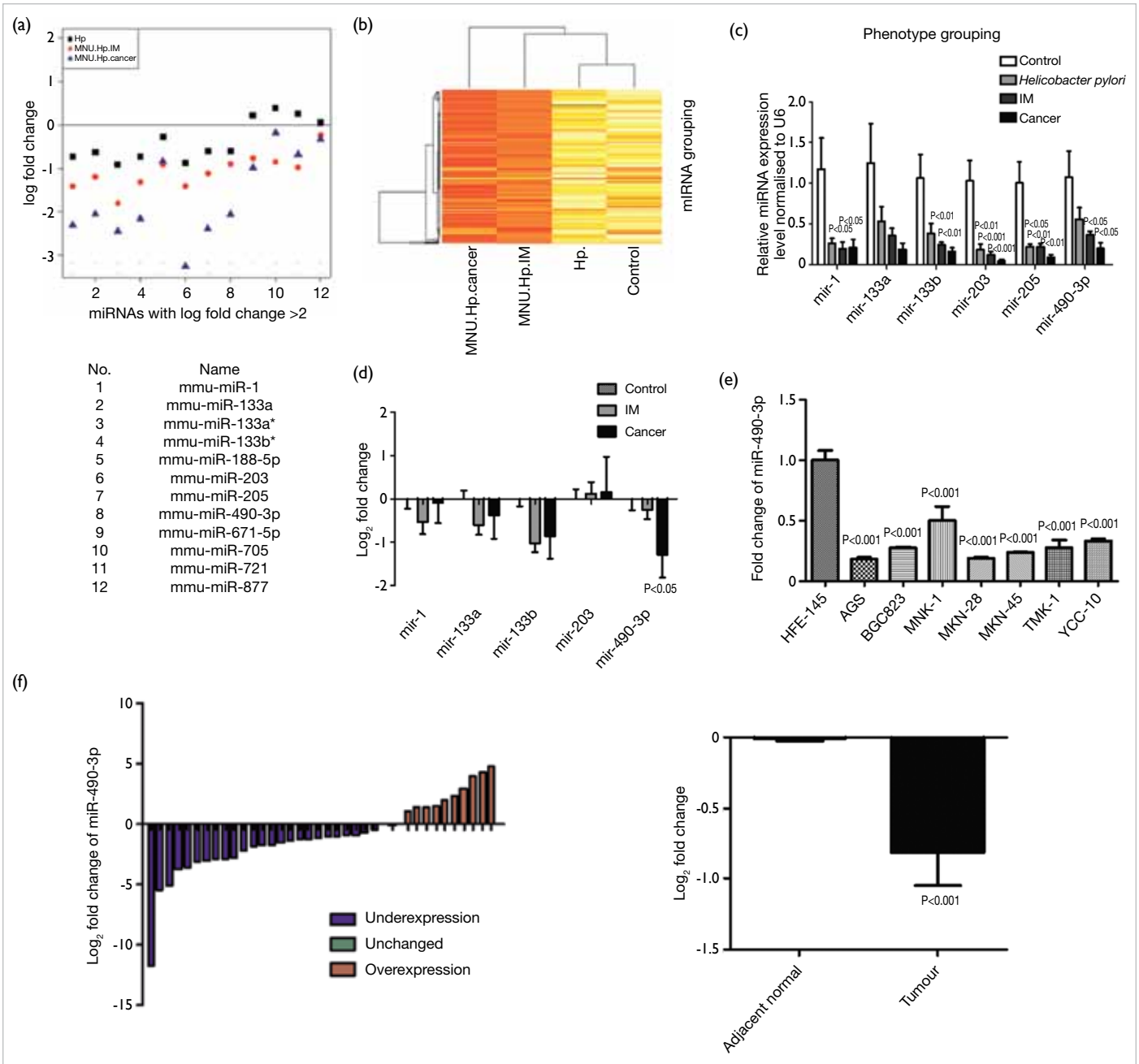


FIG 1. miR-490-3p was down-regulated in gastric cancer: (a) fold change analysis from miRNA array result, (b) heat map, (c) real-time PCR validation in mouse tissues; (d) miR-490-3p expression level in human normal, intestinal metaplasia (IM), and gastric cancer samples; (e) miR-490-3p expression level in gastric cell lines; (f) miR-490-3p expression level in paired human tissue samples showing that miR-490-3p was underexpressed, unchanged, or overexpressed in paired human tissues; and miR-490-3p was underexpressed in tumour tissues, compared with their adjacent normal tissue.

confirmed the validity of the miRNA array data. In human normal, intestinal metaplasia, and cancer tissue samples, down-regulation was found in intestinal metaplasia and cancer groups for miR-1, miR-133a, miR-133b, and miR-490-3p (Fig 1d). A gradual and significant down-regulation was observed only for miR-490-3p, which was then selected for further study.

miR-490-3p was down-regulated in human gastric cancer tissue and human gastric cancer cell lines

To further verify whether miR-490-3p was consistently down-regulated in gastric cancer, the expression level of miR-490-3p was determined in human paired tissue samples. miR-490-3p was significantly down-regulated in all gastric cancer cell

lines, compared with the normal HFE-145 (Fig 1e). miR-490-3p expression level was lower in 25 (69.4%) out of 36 pairs (Fig 1f).

miR-490-3p inhibited cell viability, migration, invasion, colony formation, and anchorage-independent cell growth

MTT assay showed that the growth of AGS and TMK-1 was significantly inhibited but the growth of normal HFE-145 was not influenced (Fig 2a). Consistently, the proliferation of AGS and TMK-1 was also significantly reduced by miR-490-3p as determined by Brdu incorporation assay (Fig 2b). MiR-490-3p inhibited cell growth by inducing cell cycle arrest (Fig 2c), which was further confirmed by western blot (Fig 2c). Overexpression of miR-490-3p also significantly inhibited migration, invasion, colony formation, and anchorage-independent cell growth in both cells (Figs 2d-g).

miR-490-3p inhibited in vivo tumour growth

We constructed lenti- miR-490-3p for *in vivo* delivery of miR-490-3p and determined its anti-tumour effect in nude mice. Compared with the control group, lenti-miR-490-3p significantly inhibited tumour size and tumour weight (Fig 2h).

DNA methylation is involved in the down-regulation of miR-490-3p in gastric cancer

In both cells' cell lines, 5AZA treatment restored the expression of miR-490-3p significantly (Fig 3a). As miR-490-3p was located in the intronic region of a host gene CHRM2 (cholinergic receptor, muscarinic 2), we hypothesised that they may share the same promoter. Correlation of miR-490-3p with CHRM2 confirmed this hypothesis (Fig 3b). Using methylation-specific PCR, DNA methylation in the promoter of CHRM2 was higher in human tumours compared with adjacent normal tissue and also higher in five of six human gastric cancer cell lines, compared with the normal gastric epithelial cell HFE-145 (Fig 3c). These findings suggest that promoter DNA methylation is at least in part responsible for the down-regulation of miR-490-3p in human gastric cancer.

SMARCD1 is a direct target of miR-490-3p

To identify the direct target of miR-490-3p, we

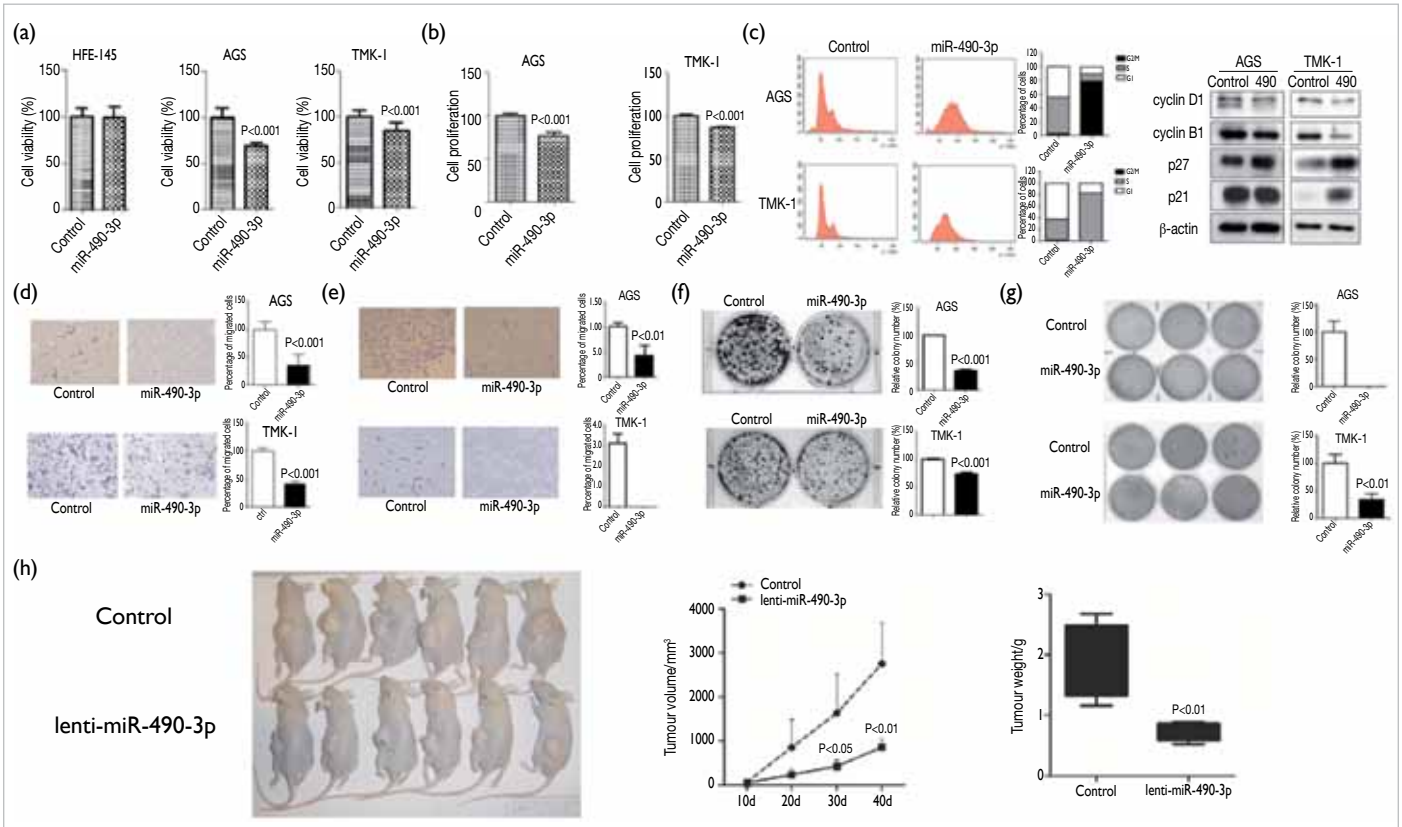


FIG 2. The tumour suppressive role of miR-490-3p *in vitro* and *in vivo*: (a) miR-490-3p inhibited cancer cell growth; (b) miR-490-3p inhibited cell proliferation as determined by Brdu assay; (c) miR-490-3p induced cell cycle arrest in AGS and TMK-1 cells in cell cycle analysis and that cell cycle arrest was confirmed by western blot; (d) miR-490-3p inhibited migration; (e) invasion assay, (f) colony formation, (g) miR-490-3p inhibited anchorage-independent cell growth; and (h) miR-490-3p inhibited tumour growth in vivo: tumour growth in nude mice and tumour volume and tumour weight.

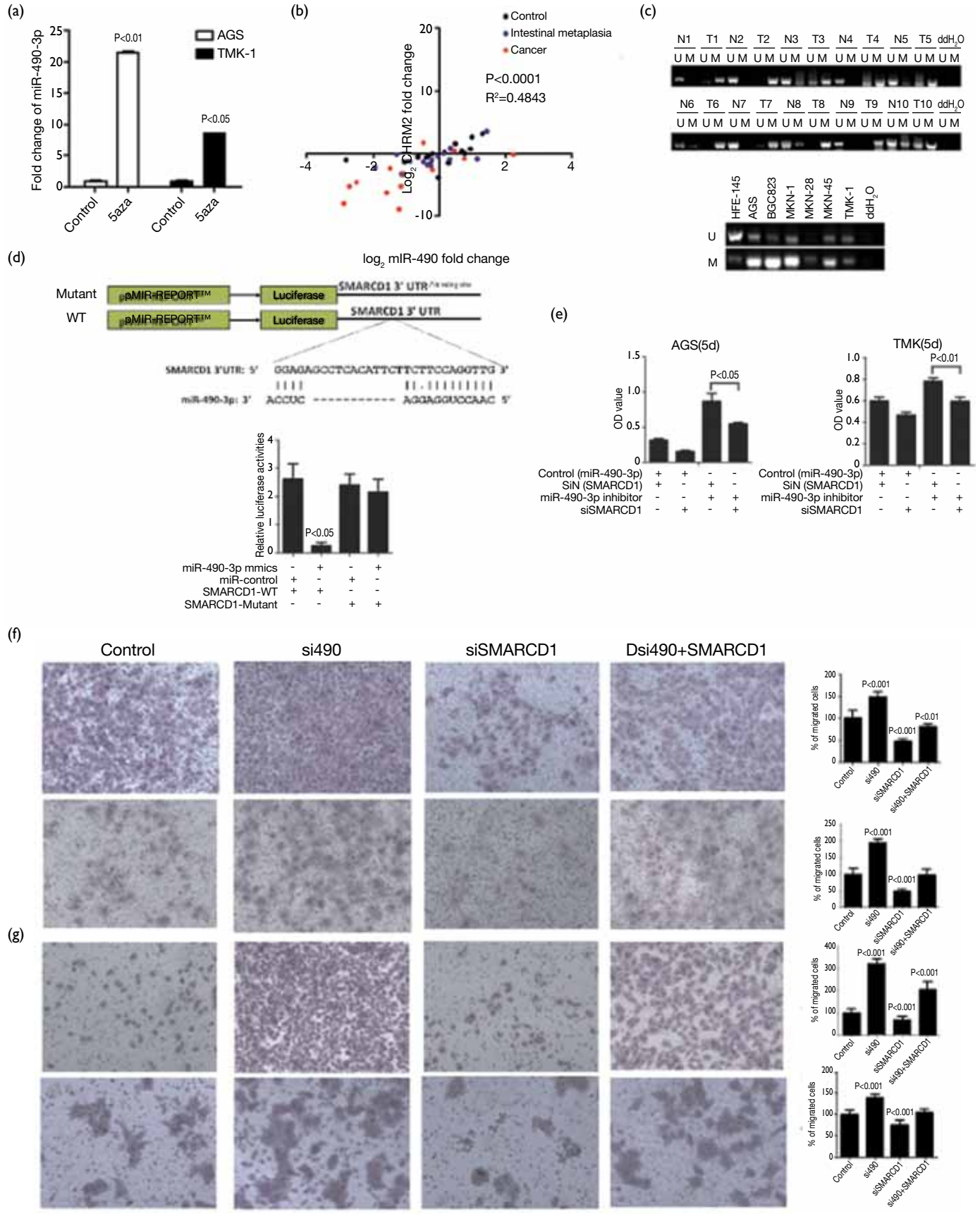


FIG 3. Upstream regulation and downstream target of miR-490-3p: (a) 5aza treatment restored miR-490-3p expression in cell lines, (b) negative correlation of miR-490-3p and CHRM2 in human tissue samples, (c) methylation-specific-PCR in tissue and cell lines, (d) dual luciferase reporter assay, and rescue experiments of (e) MTT assay, (f) cell migration, (g) cell invasion.

used a combined method of in silico prediction, whole genome mRNA array and luciferase assay. SMARCD1 was predicted to be a direct target of miR-490-3p by miRwalk and DIANA. Whole genome mRNA array using cell lines after overexpressing miR-490-3p showed a consistent down-regulation of SMARCD1 in both AGS and TMK-1 (fold change -2.056, $P<0.01$, data not shown). The array result was successfully validated by real-time PCR. Moreover, miR-490-3p reduced the SMARCD1 3'-UTR luciferase activity (Fig 3d) suggesting that miR-490-3p can target the SMARCD1 gene directly. Rescue experiments showed that the tumourigenic effect of miR-490-3p inhibitors was significantly attenuated by co-transfection of siSMARCD1 (Figs 3e-g). Taken together, these results demonstrat that SMARCD1 is a direct target of miR-490-3p.

Discussion

Despite advances in techniques to inhibit protein-coding genes using small molecules or biological agents, many cancers are unresponsive and resistant to the drugs currently used. Their potential intolerable side effects are a major concern for patients. New and more creative approaches are needed for more effective treatment of cancer. With the discovery of miRNA in 1993, miRNA became one of the important agents in cancer research and enabled development of new cancer therapeutics. In this study using a mouse model of gastric carcinogenesis, miR-490-3p was dysregulated in the development of gastric cancer; it was down-regulated in gastric, colon, bladder, and prostate cancer.

As miRNAs coordinate in cancer pathogenesis, and the phenotypical changes result from multiple interactions between miRNAs and the transcriptome, it is vital to clarify their regulating mechanisms, biological functions, and downstream targets of miR-490-3p before evaluating their usefulness in the treatment of cancer. miRNAs have clinical advantages in their use as biomarkers for diagnosis, prognosis, and treatment outcome for cancer. miR-490-3p is not only a tumour suppressor but also showed progressive down-regulation in the process of gastric carcinogenesis. It may thus be useful for early diagnosis before development of adenocarcinoma. Clinical data are still lacking to determine whether miR-490-3p is related to prognosis and treatment outcome. The experimental findings in the present study will lead to a better understanding of the cancer network regulated by miRNAs and provide new insights and opportunities in the area of miRNA research.

Acknowledgement

This study was supported by the Research Fund for the Control of Infectious Diseases, Food and Health Bureau, Hong Kong SAR Government (#10090532).

Results of this study have been published in: Shen J, Xiao Z, Wu WK, et al. Epigenetic silencing of miR-490-3p reactivates the chromatin remodeler SMARCD1 to promote *Helicobacter pylori*-induced gastric carcinogenesis. Cancer Res 2015;75:754-65.

References

1. Herrera V, Parsonnet J. *Helicobacter pylori* and gastric adenocarcinoma. Clin Microbiol Infect 2009;15:971-6.
2. Matsushima K, Isomoto H, Inoue N, et al. MicroRNA signatures in *Helicobacter pylori*-infected gastric mucosa. Int J Cancer 2011;128:361-70.
3. Saito Y, Suzuki H, Tsugawa H, et al. Dysfunctional gastric emptying with down-regulation of muscle-specific microRNAs in *Helicobacter pylori*-infected mice. Gastroenterology 2011;140:189-98.
4. He XX, Chang Y, Meng FY, et al. MicroRNA-375 targets AEG-1 in hepatocellular carcinoma and suppresses liver cancer cell growth in vitro and in vivo. Oncogene 2012;31:3357-69.
5. Chen L, Su L, Li J, et al. Hypermethylated FAM5C and MYLK in serum as diagnosis and pre-warning markers for gastric cancer. Dis Markers 2012;32:195-202.

Migration status and cardiovascular disease risks in Hong Kong adolescents

LL Hui *, MY Wong, TWH Chung, KKY Lee, CM Schooling

KEY MESSAGES

1. In Hong Kong, early childhood migrants and children of migrant women had more cardiovascular disease–related risk factors in adolescence.
2. An intergenerational transition in living condition early in life may be linked with susceptibility to cardiovascular disease–related risk factors in migrant populations or populations that undergo rapid economic development.

Hong Kong Med J 2016;22(Suppl 6):S19-23
HHSRF project number: 10111311

[1] **LL Hui**, [2] **MY Wong**, [3] **TWH Chung**, [3] **KKY Lee**, [1,4] **CM Schooling**

[1] *School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong*
[2] *Department of Mathematics, The Hong Kong University of Science and Technology*
[3] *Student Health Service, Department of Health, Hong Kong SAR, China*
[4] *CUNY School of Public Health, New York, USA*

* Principal applicant: huic@hku.hk
Corresponding author: cms1@hku.hk

Introduction

Cardiovascular diseases (CVD) are the leading cause of death worldwide and are expected to be more common in the next two decades, particularly in developing countries or migrant populations that undergo rapid economic development. This is potentially attributed to a 'mismatch' between living conditions over generations,[1] which may predispose to excess CVD risk in later life. Hong Kong has been largely composed of a migrant population from essentially pre-industrial China during the 1940-50s and more recent immigration. Migrants born in mainland China prior to the economic growth of the last 30 years were raised in very limited conditions. In the 1970s, the gross domestic product per person in China was about 12% of that in Hong Kong. Contemporary children in Hong Kong are growing up in an economically developed setting with a social infrastructure similar to western countries. They have different intergenerational experiences of economic development relative to where they were born or when their parents and grandparents migrated to Hong Kong. Understanding CVD risk among migrants and migrant generations in Hong Kong may identify target groups for effective early disease prevention.

This study built on the large population-representative Hong Kong Chinese birth cohort—'Children of 1997'—to examine the role of migration in CVD-related risk factors observed in adolescence. More specifically we examined the relation of (1) migration from China to Hong Kong at different life stages and (2) the number of generations in Hong Kong with CVD-related risk factors in adolescence. We also assessed whether associations varied by gender or were mediated by socio-economic position.

Methods

This study was approved by the University of Hong Kong-Hospital Authority Hong Kong West Cluster Joint Institutional Review Board (UW 12-320) and the Ethics Committee of the Department of Health, Government of the Hong Kong SAR, People's Republic of China.

This observational study was conducted from January 2013 to December 2013 to investigate CVD-related factors by migration status in Hong Kong adolescents born in 1997. Hong Kong (native-born) adolescents were derived from the 'Children of 1997' birth cohort,[2] a population-representative Chinese birth cohort (n=8327) that covered 88% of all births in Hong Kong in April/May 1997. Families were recruited at their first postnatal visit to a Maternal and Child Health Centre, where baseline characteristics were obtained using a self-administered questionnaire. Passive follow-up via record linkage with public health sectors and active follow-up via surveys has been started since 2005 and 2008, respectively. Migrant adolescents were born in mainland China. Staff from the Student Health Service (SHS) identified students who ever attended the SHS and who were born in 1997 elsewhere in China and migrated to Hong Kong before the age of 12 years.

Data were retrieved from the SHS records for both the birth cohort and the migrants, including weight, height, blood pressure, pubertal assessment of development of breast/genital and pubic hair and date of assessment, age at menarche, and sub-scores of the Achenbach's Youth Self-Report (YSR). Date of birth, year of migration, country of birth, and parental education attainment were also retrieved for migrants.

Exposure

The main exposure was migration status, classified by the participants' place of birth, Hong Kong (native-born) or elsewhere in China (migrants). Migrants were classified into four subgroups according to the age at migration (0-2, 2-6, 6-8, or 8-12 years). The secondary exposure was migrant generation among the native Hong Kong born (ie from the birth cohort), classified as 1st, 2nd, or 3rd+ generation migrant according to the place of birth (Hong Kong or elsewhere, mainly mainland China) of the mother and maternal grandmother (Fig 1).

Outcomes

The primary outcome was adiposity at 14 years old and blood pressure at 13 years old. The secondary outcomes were other CVD-related factors including age of puberty, tempo of height growth, and stress. Adiposity at 14 years was proxied by age and gender-specific body mass index (BMI) z-score relative to the 2007 World Health Organization growth reference, calculated from the height and weight taken between 12.5 and 15.5 years of age. For completeness we also presented the association of migration status with height z-score. Systolic and diastolic blood pressure (mm Hg) at 13 years was measured between 12.0 and 14.9 years of age on the right arm in a seated position mainly using the automated oscillometric device. Age of puberty was indicated by pubic hair development for both sexes, breast development and age at menarche for girls and genital development for boys. Tempo of height growth was proxied by height growth per year (cm/year) during 6-9, 9-12, and 12-15 years. We used the closest measurements to 6, 9, 12, and 15 years respectively for 5.0-7.5, 7.5-10.5, 10.5-13.5, and 13.5-16.5 years. Stress was proxied by internalising behaviour, externalising behaviour, anxiety/depression symptoms and social problems at age 13-14 years indicated by sub-scores of the self-administrated Achenbach's YSR. Higher scores indicated greater stress.

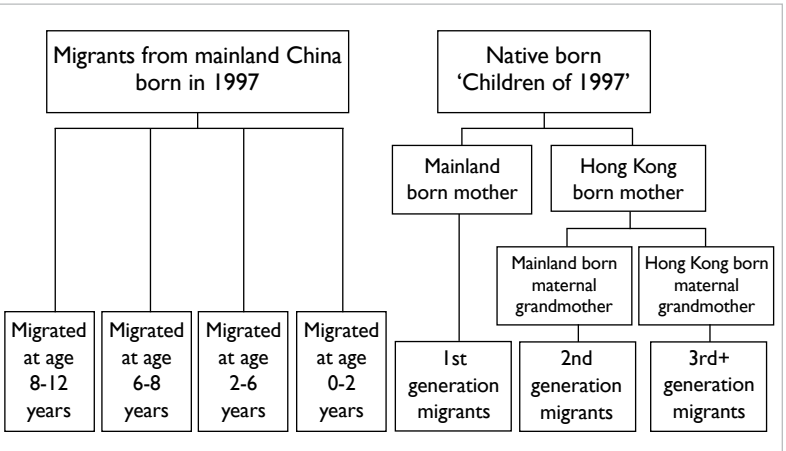


FIG 1. Classification of migration status

Statistical analysis

Multivariable linear regression was used to assess the association of migration status with BMI, blood pressure, tempo of height growth at each 3-year-period, stress, and age at menarche (girls only). Interval censored regression was used to examine the association of migration status with age at onset of puberty. We tested whether the associations varied by gender (by the significance of interaction terms), and whether these associations were mediated by family socio-economic position (proxied by the highest education attainment of both parents as ≤grade 9 or ≥grade 10 according to the Pearl's mediation formula).

Results

Participant characteristics

Of the original 8327 'Children of 1997', 8285 were alive and had not withdrawn as of 30 April 2012. Of them, 7671 (92%) had information for at least one of the CVD-related risk factors available for analysis. The SHS identified 13 245 students (6411 girls and 6834 boys) who were born in 1997 elsewhere in China and migrated to Hong Kong before aged 12 years from all students who had ever attended the SHS. Of these, 12 882 (97%) had information for at least one of the CVD-related risk factors. Respectively 10 259 (77%) and 7671 (73%) of the birth cohort members and migrants attended the SHS and had information on BMI at 14 years. Parents of adolescents who did not attend SHS at the age 12.5 to 15.5 years had similar education attainment to those who attended SHS service at least once.

Table 1 shows that 2nd and 3rd+ generation migrants had parents with similar level of education, which was higher than that of parents of 1st generation migrants. Parents of 1st generation migrants had a similar education level to migrants from mainland China. There was no difference in the distribution of parents' education attainment among migrants categorised by age at migration, except that children migrated to Hong Kong at 0-2 years had slightly higher educated parents.

Association of migration status with CVD-related risk factors

Compared with 2nd+ (2nd and 3rd+) generation migrants, migration from elsewhere in China to Hong Kong before 6 years of age was associated with faster height growth at 6-9 years, slower height growth at 12-15 years, earlier puberty, higher height z-score, higher blood pressure, and greater stress at 13-14 years in both boys and girls as well as higher BMI at 14 years in boys (Table 2). When height was adjusted, migrants and 1st generation migrants had higher diastolic but not systolic blood pressure (data not shown). These differences, except for stress, were

also observed between 1st and 2nd+ generation migrants (Table 3), but there was no difference in CVD-related risk factors between 2nd and 3rd+ generation migrants.

None of the associations of migration status with CVD-related factors was mediated by socio-economic position, except that association between migration at 0-6 years old and diastolic blood pressure was partially (20%) mediated.

Discussion

In a population-representative Hong Kong birth cohort 'Children of 1997' supplemented by migrants of the same age from elsewhere in China, we assessed the association of migration status with CVD-related factors. Most previous studies have compared migrants with a host population of different ethnicity, such that socio-cultural factors or gene-environment interactions cannot be excluded, or that comparison with non-migrants in home countries with poorer living condition cannot be made. Therefore, this fails to isolate the impact of intergenerational transition from that of the current living condition.

As previously reported, compared with 2nd+ generation migrants, 1st generation migrants were fatter, taller, and had earlier onset of puberty.[3] The present study showed that 2nd and 3rd+ generation migrants had comparable markers of cardiovascular health. However, the relation of migrant generation and CVD-related risks (bio-markers for cardiovascular health) will have to be confirmed after completion of puberty.

Migration before the age of 0-6 years was associated with higher blood pressure in both sexes, greater BMI in boys, and earlier age at menarche in girls. This suggested that migration in early childhood was associated with cardiovascular risk factors. Age at migration may be a proxy of acculturation, because time of residence increases social contacts and may be associated with the impact of migration on health, depending on the changes in behaviour, eg diet, lifestyle, and health seeking behaviour. We has previously reported that men migrated to Hong Kong in early childhood had a greater risk of developing heart disease,[4] and that the effect of migration on ischaemic heart disease mortality may differ according to the age at arrival in Hong Kong.[5] This suggested that childhood may be a critical window during which a transition of living condition may exert the greatest impact on subsequent health.

The prevalence of CVD is substantially higher among men than women. Migration from mainland China was associated with a greater BMI at 14 years in boys, although there was no gender difference in the association of migration with blood pressure and other CVD-related factors. Whether the greater BMI in boys implicates certain sex-specific acculturation process or an impact from intergenerational mismatch requires further studies in adulthood with better markers of cardiovascular health. Although migrants often have a lower socio-economic position than the general population, there was little evidence that the difference in CVD-related factors according to migration status was mediated by family socio-economic position.

Despite the large sample size, there were some limitations to this study. Attending the SHS was voluntary; nonetheless participants who were excluded due to missing data had similar parental education to those included. Although broad proxy was used for socio-economic position and parental education attainment, it positively predicted

TABLE 1. Baseline characteristics by migration status

Characteristics	Migrants (%)				Native born 'Children of 1997' (%)		
	Migrated at 8-12 years of age (n=3079)	Migrated at 6-8 years of age (n=1592)	Migrated at 2-6 years of age (n=5885)	Migrated at 0-2 years of age (n=2689)	1st generation migrant (n=3351)	2nd generation migrant (n=3733)	3rd+ generation migrant (n=1217)
Boys	50	51	53	51	53	53	52
Father's education							
≤Grade 9	57	60	62	55	60	32	36
Grade 10-11	33	32	32	37	28	37	38
≥Grade 12	9.9	8.1	6.6	8.6	12	31	27
Mother's education							
≤Grade 9	62	66	66	62	62	25	30
Grade 10-11	32	30	29.0	32	30	53	52
≥Grade 12	6.5	4.5	4.6	6.1	8.3	22	18
Parents' highest education							
≤Grade 9	51	54	54	47	48	18	21
Grade 10-11	38	37	38	42	37	46	48
≥Grade 12	12	9.2	8.5	11	15	36	30

TABLE 2. Adjusted (for age and sex) association between migration status and cardiovascular disease–related risk factors

Cardiovascular disease–related risk factors	Migrants				Native born 'Children of 1997	
	Migrated at 8-12 years of age	Migrated at 6-8 years of age	Migrated at 2-6 years of age	Migrated at 0-2 years of age	1st generation migrant	2nd+ generation migrant
Body mass index z-score at 14 years* (β [95% CI])						
All	-0.09 (-0.15, -0.03)‡	0.03 (-0.04, 0.11)	0.02 (-0.03, 0.07)	0.13 (0.07, 0.20)‡	0.06 (-0.01, 0.12)	Ref
Boys	-0.07 (-0.16, 0.02)	0.09 (-0.03, 0.21)	0.09 (0.01, 0.17)‡	0.22 (0.12, 0.32)‡	0.10 (0.00, 0.21)‡	Ref
Girls	-0.11 (-0.19, -0.04)‡	-0.03 (-0.13, 0.07)	-0.05 (-0.12, 0.01)	0.04 (-0.04, 0.12)	0.01 (-0.07, 0.09)	Ref
Height z-score at 14 years* (β [95% CI])						
All	0.02 (-0.03,0.06)	0.05 (-0.01, 0.10)	0.11 (0.07, 0.15)‡	0.14 (0.09, 0.19)‡	0.14 (0.09, 0.19)‡	Ref
Boys	0.05 (-0.02, 0.11)	0.09 (-0.00, 0.17)	0.16 (0.11, 0.22)‡	0.20 (0.12, 0.27)‡	0.17 (0.10, 0.25)‡	Ref
Girls	-0.01 (-0.07, 0.04)	0.00 (-0.07, 0.07)	0.05 (0.00, 0.10)‡	0.09 (0.03, 0.15)‡	0.10 (0.04, 0.16)‡	Ref
Blood pressure at 13 years (mmHg) [β (95% CI)]						
Systolic blood pressure	0.33 (-0.26, 0.91)	-0.17 (-0.93, 0.58)	0.69 (0.18, 1.19)‡	0.68 (0.05, 1.30)‡	0.88 (0.25, 1.51)‡	Ref
Diastolic blood pressure	0.36 (0.04, 0.68)‡	0.41 (-0.00, 0.83)	0.72 (0.44, 1.00)‡	0.58 (0.24, 0.92)‡	0.81 (0.46, 1.15)‡	Ref
Onset of puberty† (time ratio [95% CI])						
Boys						
Genital development	-	-	0.993 (0.984, 1.002)	1.003 (0.992, 1.014)	0.993 (0.983, 1.002)	Ref
Pubic hair development	-	-	0.982 (0.973, 0.991)‡	1.000 (0.985, 1.007)	0.995 (0.985, 1.001)	Ref
Girls						
Breast development	-	-	0.973 (0.964, 0.981)‡	0.980 (0.970, 0.990)‡	0.980 (0.970, 0.990)‡	Ref
Pubic hair development	-	-	0.983 (0.973, 0.993)‡	0.992 (0.979, 1.005)	0.993 (0.982, 1.004)	Ref
Age at menarche (β [95% CI])	-0.00 (-0.08, 0.07)	-0.13 (-0.23, -0.04)‡	-0.24 (-0.30, -0.17)‡	-0.16 (-0.24, -0.09)‡	-0.17 (-0.25, -0.09)‡	Ref
Height growth† (cm/year) [β (95% CI)]						
6-9 years	-	-	0.19 (0.14, 0.22)‡	0.15 (0.10, 0.19)‡	0.11 (0.06, 0.15)‡	Ref
9-12 years	-	0.03 (-0.05, 0.10)	0.04 (-0.01, 0.09)	0.05 (-0.01, 0.11)	0.02 (-0.04, 0.08)	Ref
12-15 years	-	-0.10 (-0.22, 0.03)	-0.27 (-0.36, -0.19)‡	-0.20 (-0.31, -0.10)‡	-0.15 (-0.26, -0.05)‡	Ref
Stress at 13-14 years† (β [95% CI])						
Internalising behaviour	-	-	0.83 (0.41, 1.25)‡	0.87 (0.38, 1.35)‡	0.33 (-0.14, 0.81)	Ref
Externalising behaviour	-	-	0.49 (0.16, 0.82)‡	0.79 (0.40, 1.17)‡	0.14 (0.23, 0.52)‡	Ref
Anxious/depressive	-	-	0.47 (0.22, 0.72)‡	0.55 (0.26, 0.83)‡	0.26 (-0.02, 0.54)	Ref
Social problem	-	-	0.17 (0.52, 0.29)‡	0.18 (0.04, 0.31)‡	-0.04 (-0.18, 0.09)	Ref

* Reference to the World Health Organization 2007 growth reference

† Analysis limited to migrants who came to Hong Kong before 6 or 8 years old because such information in those who migrated at older ages might have missed

‡ P<0.05

household income in the birth cohort. Information on potential mediators such as diet and physical activities was not available for the migrants and could not be analysed.

Conclusion

Early childhood migrants and children of migrant women had more CVD-related risk factors in adolescence. The impact of migration on cardiovascular health may be gender-specific and time-specific, with transition during early childhood being more important. Our findings highlight the need to assess the role of early intervention strategies at both individual and population levels in promoting cardiovascular health in Hong Kong adolescents.

Acknowledgements

This study was supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (#10111311). The 'Children of 1997' birth cohort was initially supported

TABLE 3. Adjusted (for age and sex) association between migrant generations and cardiovascular disease–related factors

Cardiovascular disease–related risk factors	Native born 'Children of 1997'		
	1st generation migrant	2nd generation migrant	3rd+ generation migrant
Body mass index z-score at 14 years* (β [95% CI])			
All	0.06 (-0.03, 0.16)	-0.02 (-0.12, 0.08)	Ref
Boys	0.13 (-0.02, 0.29)	0.00 (-0.17, 0.17)	Ref
Girls	-0.01 (-0.13, 0.11)	-0.03 (-0.16, 0.10)	Ref
Height z-score at 14 years* β [95% CI])			
All	0.16 (0.09, 0.23)†	0.02 (-0.05, 0.10)	Ref
Boys	0.22 (0.11, 0.32)†	0.07 (-0.04, 0.17)	Ref
Girls	0.10 (0.00, 0.19)†	-0.02 (-0.12, 0.08)	Ref
Blood pressure at 13 years (mm Hg) [β (95% CI)]			
Systolic blood pressure	1.06 (0.12, 1.99)†	0.21 (-0.78, 1.21)	Ref
Diastolic blood pressure	0.95 (0.45, 1.45)†	0.11 (-0.40, 0.62)	Ref
Onset of puberty† (time ratio [95% CI])			
Boys			
Genital development	0.999 (0.985, 1.013)	1.007 (0.992, 1.021)	Ref
Pubic hair development	0.992 (0.976, 1.007)	0.998 (0.982, 1.015)	Ref
Girls			
Breast development	0.981 (0.968, 0.994)†	0.999 (0.986, 1.014)	Ref
Pubic hair development	0.993 (0.977, 1.009)	1.002 (0.986, 1.019)	Ref
Age at menarche (β [95% CI])	-0.13 (-0.25, -0.01)†	0.01 (-0.12, 0.13)	Ref
Height growth (cm/year) [β (95% CI)]			
6-9 years	0.08 (0.01, 0.15)†	-0.02(-0.10, 0.05)	Ref
9-12 years	0.02 (-0.07, 0.10)†	-0.00 (-0.09, 0.09)	Ref
12-15 years	-0.21 (-0.35, -0.07)†	-0.04 (-0.18, 0.11)	Ref
Stress at 13-14 years (β [95% CI])			
Internalising behaviour	0.04 (-0.65, 0.73)	-0.09 (-0.77, 0.60)	Ref
Externalising behaviour	0.23 (-0.27, 0.74)	0.10 (-0.49, 0.69)	Ref
Anxious/depressive	0.18 (-0.21, 0.56)	0.08 (-0.31, 0.47)	Ref
Social problem	-0.08 (-0.29, 0.14)	-0.01 (-0.23, 0.22)	Ref

* Reference to the World Health Organization 2007 growth reference
† P<0.05

by the Health Care and Promotion Fund, Health and Welfare Bureau, Hong Kong SAR Government (# 216106) and re-established in 2005 with support from the Health and Health Services Research Fund (#03040771), and the University Research Committee Strategic Research Theme of Public Health, The University of Hong Kong. The authors thank colleagues at the Student Health Service and Family Health Service of the Department of Health for their assistance and collaboration. They also thank the late Dr Connie O for coordinating the project and all the fieldwork for the initial study in 1997-8.

References

1. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science 2004;305:1733-6.
2. Schooling CM, Hui LL, Ho LM, Lam TH, Leung GM. Cohort profile: 'Children of 1997': a Hong Kong Chinese birth cohort. Int J Epidemiol 2012;41:611-20.
3. Hui LL, Leung GM, Lam TH, Schooling CM. Inter-generational influences on age at onset of puberty: Hong Kong's 'Children of 1997' birth cohort. Int J Epidemiol 2012;41:292-300.
4. Schooling M, Leung GM, Janus ED, Ho SY, Hedley AJ, Lam TH. Childhood migration and cardiovascular risk. Int J Epidemiol 2004;33:1219-26.
5. Schooling CM, Lam TH, Ho SY, Mak KH, Leung GM. Does economic development contribute to sex differences in ischaemic heart disease mortality? Hong Kong as a natural experiment using a case-control study. BMC Public Health 2008;8:32.

Effect of combined use of *Fructus Schisandrae* and statin on high-fat-diet-induced metabolic syndrome in rats

E Wat, CF Ng, CL Liu, C Zhang, CM Koon, CP Lau, CW Wong, KY Pang, X Zhang, KP Fung, CBS Lau, PC Leung *

KEY MESSAGES

1. The combined use of *Fructus Schisandrae* aqueous extract (FSE) and atorvastatin (AS) exerts no further synergistic effect on diet-induced non-alcoholic fatty liver disease in rats, compared with rats given AS alone.
2. The use of FSE can protect high-fat-fed rats from AS-induced liver toxicity.
3. Preliminary pharmacokinetic studies suggest that FSE can enhance plasma metabolites of AS but reduce the liver metabolites of AS.

Hong Kong Med J 2016;22(Suppl 6):S24-7
HHSRF project number: 09100241

[1,2] **E Wat**, [1,2] **CF Ng**, [1,2] **CL Liu**, [1,2] **C Zhang**, [1,2] **CM Koon**, [1,2] **CP Lau**, [1,2] **CW Wong**, [1,2] **KY Pang**, [1,2] **X Zhang**, [1,2,3] **KP Fung**, [1,2] **CBS Lau**, [1,2] **PC Leung**

The Chinese University of Hong Kong
[1] *Institute of Chinese Medicine*
[2] *State Key Laboratory of Phytochemistry & Plant Resources in West China (CUHK)*
[3] *School of Biomedical Sciences*

* Principal applicant and corresponding author: pingcleung@cuhk.edu.hk

Introduction

3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, also known as statins, are the best-selling class of prescription drug in the world. Statins inhibit the reduction of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonic acid, thus reducing cholesterol production. They are beneficial to patients of different ages and genders with moderate and high cardiovascular disease risk; nonetheless no drug is without potential adverse effects.[1]

Fructus Schisandrae, the fruit of *Schisandrae chinensis*, is a traditional Chinese herb believed to be a liver tonic. Extracts isolated from *Fructus Schisandrae* can alleviate hepatic cholesterol and triglyceride levels, and attenuate the development of fatty liver in rodents fed a high-fat diet.[2] Preliminary pharmacokinetic study has been performed to determine whether the combined use of *Fructus Schisandrae* aqueous extract (FSE) and atorvastatin (AS) affects the plasma or liver concentration of AS and/or its metabolites in high-fat-fed rats.

The present study, conducted from January 2012 to December 2013, aimed to determine whether the combined use of FSE and AS would be hepatoprotective by (1) improving high-fat diet-induced non-alcoholic fatty liver, and (2) reducing the side effects of taking statin alone, including increased incidence of elevated liver enzymes and liver toxicity.

Methods

Fructus Schisandrae and statin

Fructus Schisandrae was purchased from 致信 in Guangzhou, China. Chemical authentication was performed in accordance with the Chinese Pharmacopoeia 2010. Extraction of *Fructus Schisandrae* was by boiling in water. The aqueous extracts were combined and filtered. Filtrate was concentrated under reduced pressure at 60°C. The concentrated extract was frozen and lyophilised to dryness. The percentage yield was 48.7% w/w. Herbarium voucher specimen of *Fructus Schisandrae* was deposited at the museum of the Institute of Chinese Medicine at the Chinese University of Hong Kong (No.: 2012-3357). In addition, AS calcium (purity 99%) was purchased from ZheJiang Dankong Pharmaceutical.

Animal study 1

All experiments were carried out in accordance with the guidelines approved by the Animal Research Ethics Committee at the Chinese University of Hong Kong (No.: 11/004/MIS-5). Male Sprague Dawley rats weighing 200-210 g were purchased from the Laboratory Animal Services Centre of the Chinese University of Hong Kong.

Study 1 was performed to determine the combined effect of FSE and AS on diet-induced non-alcoholic fatty liver disease. All rats were housed in standard cages at a constant temperature of 21°C with a 12-hour light-dark cycle. Animals were randomly divided into three groups (n=8-10) and fed a high-fat diet (21% fat and 0.15% cholesterol) and one of three supplements: (1) distilled water, (2) 0.3% AS, or (3) 0.3% AS + 0.45% FSE.

After 8 weeks, all rats were sacrificed after a 16-hour overnight fast. Animals were anaesthetised

with a mixture of ketamine (100 mg/kg) and xylazine (10 mg/kg) intraperitoneally. Blood was withdrawn by cardiac puncture. Plasma was collected and the livers excised and stored at -80°C until analysis. Plasma aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT) activities were determined by a kinetic method using ALT/SGPT Liqui-UV Test and AST/SGOT Liqui-UV Test (Stanbio Laboratory, TX, USA). Total liver lipids were determined gravimetrically after extraction by the method of Bligh and Dyer.[3]

For liver glutathione peroxidise measurement, liver tissues were rinsed with PBS, pH 7.4 and homogenised in 5-10 mL cold buffer (50 mM Tris-HCl, pH 7.5, 5 mM EDTA, and 1 mM dithiothreitol). Homogenates were centrifuged at 10 000 g for 15 minutes at 4°C. Supernatant was removed and assayed for GPx activity using a commercially available kit (Cayman Chemical, USA) according to the manufacturer's instructions.

Mitochondrial permeability transition was assessed using mitochondrial fractions from liver samples prepared according to the commercially available kit (Millipore, USA). The mitochondrial fractions were incubated with buffer containing 125 mM sucrose, 65 mM KCl, 10 mM HEPES (pH 7.2), 5 mM succinate (freshly prepared), and 5 mM rotenone (freshly prepared), and were mixed with cyclosporine A (5 μM in 0.5% ethanol final concentration). The mixtures were incubated for 5 minutes at 30°C, followed by calcium chloride solution (1 μM final concentration) at 30°C for another 5 minutes. Absorbance was measured at 520 nm. The swelling reaction was started by addition of K_3PO_4 (0.5 mM, pH 7.2), and absorbance was read every 2 minutes for 30 minutes at 30°C. The extent of mitochondrial swelling was assessed by measuring the total area under the swelling reaction curve and was expressed as % relative to control group.

Reactive oxidant species were measured from mitochondrial fraction (50 μg protein/ml) using DCFDA solution (Invitrogen, USA). Fluorescence intensity was measured every 5 minutes for 60 minutes by Biorad Fluostar Optima 413-101 BMG Fluorescent Microplate Reader at 485 nm excitation and 520 nm emission. Levels were expressed as % relative to control group.

Animal study 2

To study the pharmacokinetics between AS and FSE, high-fat-fed Sprague Dawley rats were given distilled water or FSE for 1 week, followed by one dose of AS or distilled water on the day of blood and liver collection. FSE or AS were given intragastrically (instead of diet supplementation) to provide a more accurate dose. The dose of AS and FSE was calculated so that it was equivalent to the AS diet supplementation dose of 0.3% and FSE supplementation dose of 0.45%. The animals were randomly divided into three groups (n=4-6) and fed a high-fat diet and one of the three treatments intragastrically: (1) 200 mg/kg AS, (2) 0.6 g/kg FSE, or (3) 200 mg/kg AS + 0.6g/kg FSE.

To measure drug/herb concentration within the blood, blood samples (200 μl) were collected at time 0 (control), 0.5, 1, 2, 4, 6, and 8 hours. Blood samples were centrifuged and plasma samples (100 μl) were stored at -80°C until LC-MS analysis. For measurement of the liver herb/drug concentration, livers were collected at time 0 (control), 0.5, 1, and 2 hours. Liver samples were quickly snap frozen with liquid nitrogen and stored at -80°C until analysis.

Plasma and liver concentration of AS, ortho-hydroxy AS, para-hydroxy AS, schiszandrin was measured using an electrospray ionisation LC-MS, using hesperetin as the internal standard. Plasma samples containing herb/drug were prepared as previously described.[4] Extracted samples were sent for LC-MS analysis. Liver samples were homogenised in saline, followed by mixing with acetonitrile, vortexing, and sonication (5 minutes). Samples were centrifuged at 3000 rpm (5 minutes) and supernatant was sent for LC-MS analysis. LC-MS was conducted according to the conditions previously described, using AS, AS metabolites: ortho-hydroxy AS, para-hydroxy AS, and FSE markers: schizandrin as the markers.

Statistical analysis

The differences between treatment and control groups were compared using one-way analysis of variance followed by the post-hoc Bonferroni multiple comparison test. All statistical analyses were performed using GraphPad Prism Version 5.0c (GraphPad, USA). A P value of <0.05 was considered statistically significant.

Results

Figure 1 shows the effect of 0.3% AS or combined use of 0.3% AS and 0.45% FSE on liver weight in high-fat-fed rats. AS resulted in a significant reduction in liver size in rats fed a high-fat diet. Nonetheless, the combined use of 0.3% AS and 0.45% FSE did not significantly augment this effect on liver weight, compared with AS alone. There was no significant difference in total liver lipid levels between rats with 0.3% AS and rats with 0.3% AS + 0.45% FSE (data not shown). These results indicated that the combined use of FSE with AS exerted no further beneficial effect on diet-induced non-alcoholic fatty liver disease (NAFLD), compared with AS alone.

Although FSE appeared to exert no synergistic effect with AS on diet-induced NAFLD, FSE in combination with AS exerted significant protective effects on AS-induced liver toxicity by: (1) reducing liver enzyme (ALT and AST) levels, (2) improving

liver glutathione level, (3) reducing liver reactive oxidative species, and (4) a trend of reducing calcium-induced membrane permeability transition within the liver (data not shown).

To determine whether FSE would affect the plasma and liver concentrations of AS and its metabolites during their combined use, a preliminary pharmacokinetic study was performed. Figure 2 shows the effect of the combined use of FSE and AS on plasma AS and its metabolite concentrations. The combined use of 0.3% AS and 0.45% FSE induced a significant increase in plasma AS concentration (Fig 2a). The plasma concentrations of ortho-hydroxy AS and para-hydroxy AS, two of the metabolites from AS (Figs 2b and 2c), were also increased. There were no detectable levels of schizandrin in the plasma of any group.

Figure 3 shows the effect of the combined use of AS and FSE on the liver AS and its metabolites. The combined use of 0.3% AS and 0.45% FSE significantly reduced liver AS and its metabolites, compared with 0.3% AS alone. The combined use of 0.3% AS and 0.45% FSE significantly reduced the level of liver schizandrin, compared with 0.45% FSE alone.

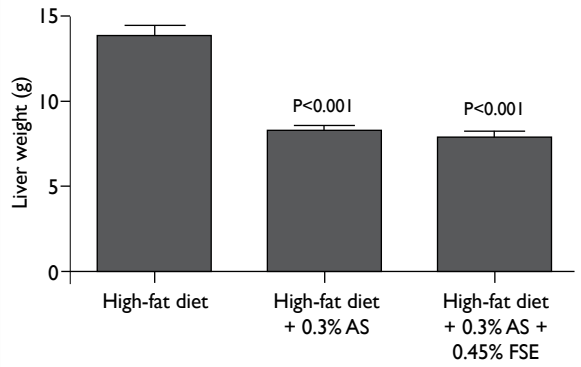


FIG 1. Effect of atorvastatin (AS) with or without Fructus Schisandrae aqueous extract (FSE) on liver size in high-fat-fed rats

Discussion

Combined use of FSE and AS exerted no further synergistic effect on diet-induced NAFLD in rats, compared with AS alone. Nonetheless, FSE could exert a potent protective effect on statin-induced toxicity. One possibility for the absence of a synergistic effect of FSE and AS on diet-induced NAFLD could be the very high dose use of AS. The use of AS alone may have optimal beneficial effects and its combined use with FSE may exert no further beneficial effect on diet-induced NAFLD. In addition, there are concerns about the adverse effects of statins on the liver. Clinically, a mild-to-moderate increase in liver transaminases is a common side effect that is regularly monitored in patients prescribed with statin. The ability of dietary FSE supplementation to exert a potent hepatoprotective effect on AS-induced liver toxicity offers great potential.

The preliminary pharmacokinetic studies of AS and FSE suggested that their combined use may enhance the concentrations of AS and its metabolites, ortho-hydroxy AS and para-hydroxy AS within the plasma. The concentrations of AS and its metabolites were reduced in the livers of rats given a combination of FSE and AS, compared with those given AS alone. AS requires CYP3A4 for metabolism. Our results indicated that FSE could enhance AS concentration within the plasma. Although the exact mechanism is unknown, it is possible that schizandrin, which requires CYP3A4 for metabolism, competes with AS

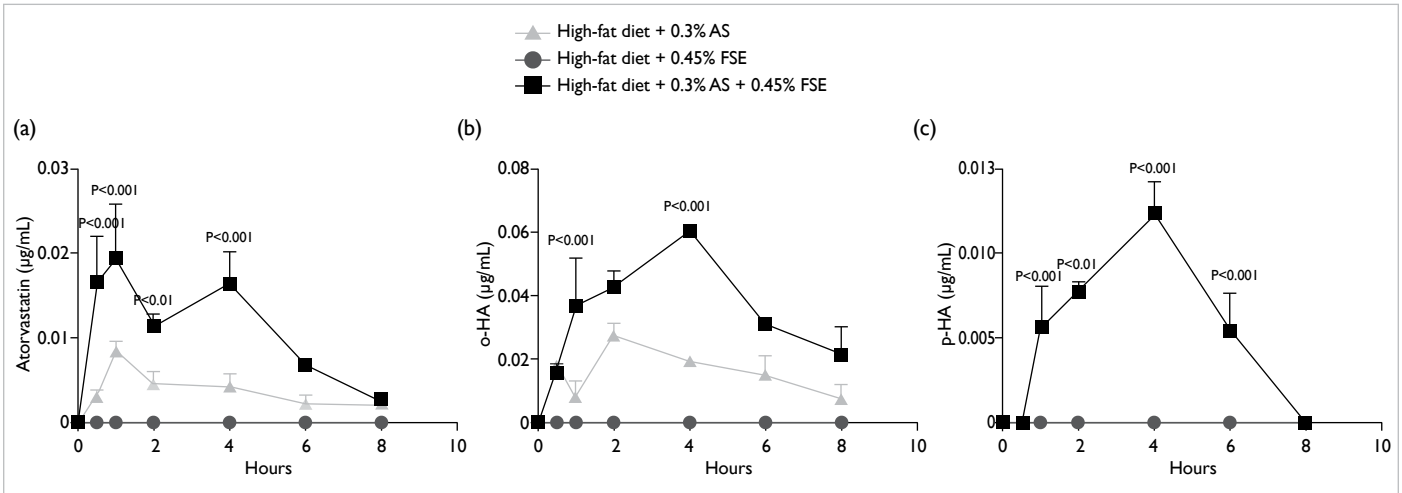


FIG 2. Effect of the combined use of atorvastatin (AS) and *Fructus Schisandrae* aqueous extract (FSE) in rats on plasma concentrations of (a) AS, (b) orthohydroxy AS (o-HA), and (c) para-hydroxy AS (p-HA). There was no detectable plasma level of schizandrin in any rat.

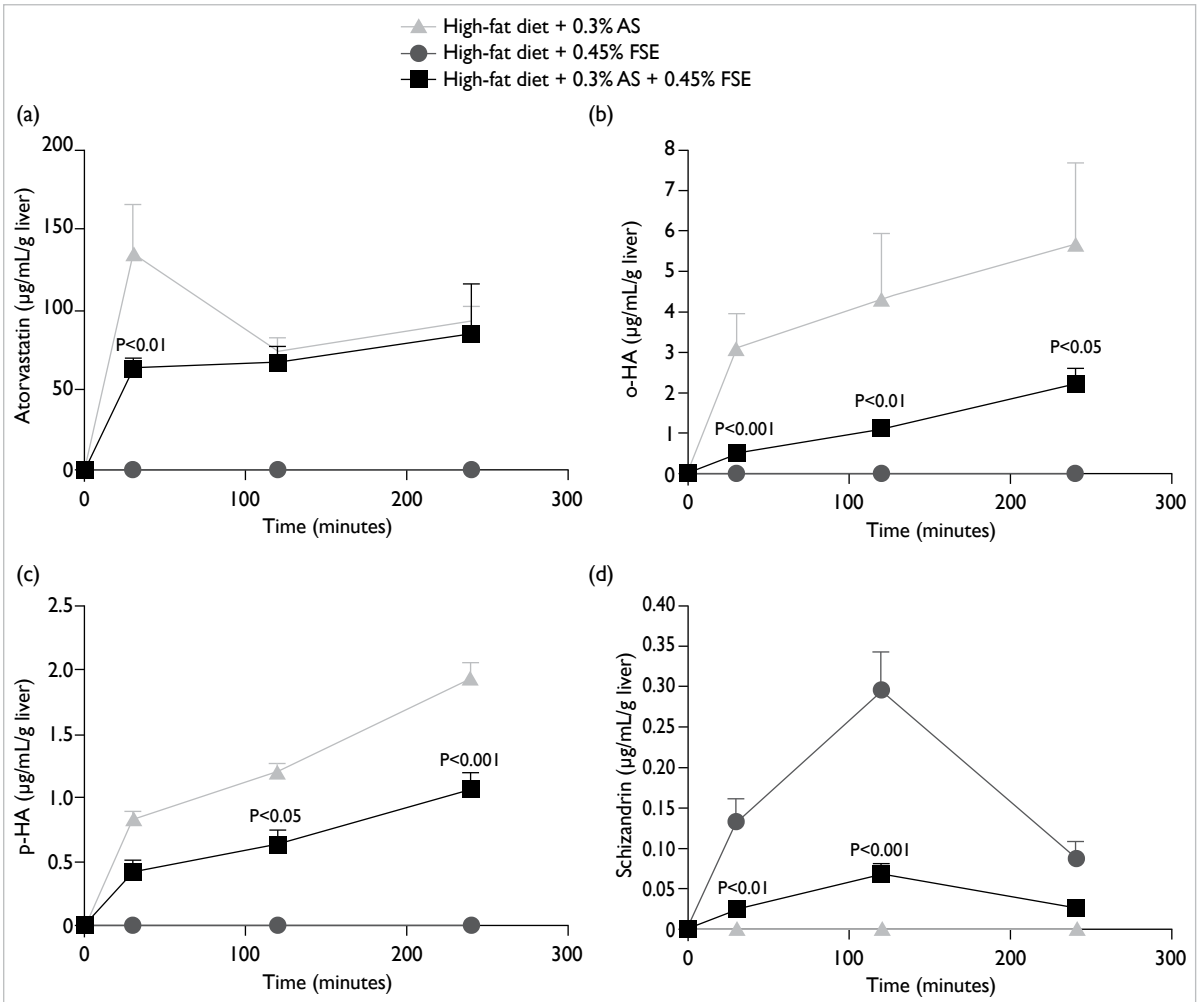


FIG 3. Effect of the combined use of atorvastatin (AS) and *Fructus Schisandrae* aqueous extract (FSE) on rat's liver concentrations of (a) AS, (b) orthohydroxy AS (o-HA), (c) para-hydroxy AS (p-HA), and (d) schizandrin.

for CYP3A4 metabolism and leads to accumulation of AS and its metabolites in the plasma. Nonetheless, schizandrin is only a weak inhibitor of CYP3A4,[5] as is its inhibitory effect on the metabolism of AS.

Our preliminary pharmacokinetic study could not explain the exact mechanism by which FSE interacts with AS to affect the plasma and liver concentrations of AS and/or its metabolites. Further studies are needed to determine whether the combined use of FSE and AS is safe in humans.

Conclusion

Combined use of FSE with AS exerts no further synergistic effect on diet-induced NAFLD in rats compared with AS alone. Nonetheless, the use of FSE can protect high-fat-fed rats from AS-induced liver toxicity. FSE may enhance plasma metabolites of AS but reduce the liver metabolites of AS. Further studies are warranted to determine the safety and underlying mechanism of the protective effects of FSE on AS-induced toxicity.

Acknowledgement

This study was supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (#09100241).

References

1. Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. Am J Cardiovasc Drugs 2008;8:373-418.
2. Pan SY, Dong H, Zhao XY, et al. Schisandrin B from Schisandra chinensis reduces hepatic lipid contents in hypercholesterolaemic mice. J Pharm Pharmacol 2008;60:399-403.
3. Bligh EG, Dyer WJ. A rapid method of total lipid extraction and purification. Can J Biochem Physiol 1959;37:911-7.
4. Hermann M, Christensen H, Reubsaet JL. Determination of atorvastatin and metabolites in human plasma with solid-phase extraction followed by LC-tandem MS. Anal Bioanal Chem 2005;382:1242-9.
5. Iwata H, Tezuka Y, Kadota S, Hiratsuka A, Watabe T. Identification and characterization of potent CYP3A4 inhibitors in Schisandra fruit extract. Drug Metab Dispos 2004;32:1351-8.

Psychometric properties of a Chinese version of the Level of Expressed Emotion scale and expressed emotion of family members perceived by patients with severe mental illness

WT Chien *, ZCY Chan, SWC Chan, LK Yip, G Ip

KEY MESSAGES

1. The psychometric properties of the Chinese version of the Level of Expressed Emotion scale revealed a high level of reliability and validity in a large convenience sample of Chinese outpatients with severe mental illness in Hong Kong.
2. The level of expressed emotion (EE) of family members perceived by patients with severe mental illness was moderate, and that perceived by patients with unipolar disorder was highest, particularly for intrusiveness/hostility and emotional involvement.
3. The level of EE of family members perceived by patients with severe mental illness differed significantly across countries, indicating possible cultural influence.

Hong Kong Med J 2016;22(Suppl 6):S28-34
HHSRF project number: 09101481

[1] **WT Chien**, [1] **ZCY Chan**, [2] **SWC Chan**, [1] **LK Yip**, [3] **G Ip**

[1] *School of Nursing, The Hong Kong Polytechnic University, Hong Kong*
[2] *Alice Lee Centre for Nursing Studies, National University of Singapore, Singapore*
[3] *Kwai Chung Hospital, Hospital Authority, Hong Kong*

* Principal applicant and corresponding author: wai.tong.chien@polyu.edu.hk

Introduction

Expressed emotion (EE) refers to the amount of (1) criticism, (2) hostility, (3) positive remarks, (4) warmth, and (5) emotional over-involvement expressed in family relationships, particularly among relatives of a psychiatric patient.[1] Of the five components, criticism, hostility, and emotional over-involvement are most predictive of patient's relapse and course of illness (particularly in patients with schizophrenia or mood disorders), and are associated with patient's symptoms, compliance with medication, family burden, and functioning.[2]

The traditional measurement tools including Camberwell Family Interview (CFI) and Five-Minute Speech Samples rate the attitudes and feelings expressed towards a patient by a main caregiver. Nonetheless, their application is limited by the lengthy training and administration required, the complex scoring system, and the availability of a key relative.[1] Patients should be the focus of assessment when trying to understand their perception of the relationship with and attitudes of their family.[2] For example, comments and emotions expressed by family members may be perceived by the patient as signs of love and care or coercive attempts to restore his/her desirable social behaviour.[2]

A self-report, 60-item Level of Expressed Emotion (LEE) scale[3] is the only valid instrument that addresses the EE perceived by patients about their own behaviour.[1,2] The scale has satisfactory correlation with the CFI and high accuracy when asking patients about their perception of EE with careful consideration given to the influence of psychotic symptoms. As the components of EE and their relative intensities are most likely to vary across cultures, the EE of family members perceived by patients with mental illness has not been adequately considered from a cultural perspective, particularly so in Chinese populations that have strong values of interdependence, collective action, and obligation of family care.[3,4]

The LEE scale has been translated into Chinese and reduced from 60 to 52 items. Its content and construct validity and internal consistency have been found satisfactory in a convenience sample of Hong Kong Chinese patients with schizophrenia.[4] The present study further examined the psychometric properties of the Chinese version of the LEE scale and the level of EE of family members perceived by Chinese patients with severe mental illness (SMI) in Hong Kong.

Methods

This study was conducted from November 2011 to October 2012. It aimed to validate a Chinese version of the LEE scale. In phase 1, semantic equivalence of the original English and translated Chinese version and test-retest reliability of the Chinese version

were examined. In phase 2, patients with SMI (schizophrenia, psychotic disorders, unipolar and bipolar disorders, and personality disorders) and one of their family caregivers were asked to complete a set of questionnaires twice over a 6-month period to examine the internal consistency, reproducibility, responsiveness, and construct validity of the Chinese version. These data were also used to examine the level of EE of family members perceived by patients with different subtypes of SMI.

Subjects were recruited from one regional psychiatric outpatient clinic serving about 5000 outpatients in Kowloon West Hospital Cluster of Hospital Authority. In phase 1, two convenience samples of 40 patients with SMI were asked to complete both Chinese and English versions of the LEE scale to test the semantic equivalence of the two versions and assess the test-retest reliability over a 2-week interval. In phase 2, a convenience sample of about 350 Chinese outpatients with SMI (at least five subjects per item for factor analyses) and one of their main family caregivers were invited to participate. This sample size allowed a ±0.05 sampling error with 95% confidence interval, with a power of 0.80 and a potential non-response rate of 20%.

Inclusion criteria were: (1) patients aged ≥18 years and living with one or more family members over the last 3 months, (2) primarily diagnosed by a psychiatrist with one type of SMI, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, and (3) able to understand Chinese/Mandarin and complete the questionnaire. Patients were excluded when they had co-morbidity of any other mental or chronic physical illness, were mentally unstable, or had been discharged from a psychiatric unit within the last month. The main family caregiver referred to a family member (aged ≥18 years and living with patient and without mental illness or cognitive impairment) who was responsible for most of the patient's daily care and considered by the patient as his/her key carer.

Instruments and data collection

In phase 2, six research instruments were used, including the Chinese version of LEE scale, Family Assessment Device (FAD), Family Burden Interview Schedule (FBIS), Beck's Depression Inventory-II (BDI-II), Beck's Anxiety Inventory (BAI), and eight items of the Brief Psychiatric Rating Scale (BPRS) for positive symptoms. All scales demonstrated satisfactory internal consistency and construct validity.[1,4]

Each patient completed the self-report questionnaire (the Chinese version of LEE scale and demographic data sheet) and returned it in a sealed envelope. When attending a psychiatric consultation, the psychiatrist used the BPRS, BDI-II, and BAI to assess the patient's psychiatric symptoms. The caregivers were interviewed by a research assistant by telephone using FBIS and FAD. Both parties completed the same questionnaires twice over 6 months.

Data analysis

The item equivalence between the Chinese and English version of the LEE scale was evaluated using weighted kappa, and their total scale/subscale equivalences were assessed by intraclass correlation coefficient using one-way ANOVA test. Pearson's product-moment correlation test was used to evaluate the test-retest reliability of the Chinese version after a 2-week interval, and its internal consistency was tested using Cronbach's alpha coefficient.

Only patients who reported no major changes in either the symptom severity or family functioning after 6 months were used to assess the reproducibility of the Chinese version, and intraclass correlation was calculated using random effects one-way ANOVA. Responsiveness of the LEE scale to change in symptom severity was evaluated by: (1) observed change for two measurements (mean difference [test 1 minus test 2]) and (2) effect sizes (observed change divided by standard deviation of baseline score), examining whether the change in LEE mean scores followed the expected change patterns in severity of symptoms, depression, and/or anxiety scores.

Construct validity was established by: (1) testing the correlation between the Chinese version and other measures with relevant theoretical constructs (FAD and FBIS) using Pearson's correlation test; and (2) using exploratory and confirmatory factor analyses to generate and conclude the factor solution as explained by the scale items using LISREL 9.1. The level of EE perceived by patients was compared between subgroups of SMI to determine their perceived family attitude and emotional environment.

Results

Phase 1

Two convenience samples of 40 patients with SMI were recruited: one group for equivalence testing and another for assessing test-retest reliability. Refusal rates were 13% and 15%, respectively, mainly due to time constraints and unwillingness to expose their mental condition.

The overall scale and 52 items of the Chinese version of the LEE scale indicated substantial agreement and thus good semantic equivalence with the original English version. 47 items had a kappa >0.85 (range, 0.86-0.95) and the remaining five (items 20, 27, 37, 48, and 50) had a kappa value between 0.76 and 0.82. Intraclass correlation coefficient between the two versions was 0.90 (P=0.01) for the

TABLE 1. Characteristics of patients with severe mental illness and family caregivers who did or did not respond*

Characteristics	Respondents (n=262)	Non-respondents (n=59)	χ^2 or *t* value
Patients			
Gender			2.08
Female	102 (38.9)	22 (37.3)	
Male	160 (61.1)	37 (62.7)	
Age (years)	29.12±10.05 (19-45)	29.45±8.91 (20-46)	1.12
Education level			2.19
Primary or below	30 (11.5)	6 (10.2)	
Secondary	181 (69.1)	42 (71.2)	
Tertiary	51 (19.5)	11 (18.6)	
Duration of mental illness (months)	35.21±14.25 (12-98)	32.90±17.02 (14-96)	1.98
Primary psychiatric diagnosis			1.58
Bipolar affective disorders	12 (4.6)	3 (5.1)	
Psychotic disorders	50 (19.1)	13 (22.0)	
Schizophrenia	118 (45.0)	26 (44.1)	
Unipolar affective disorders (eg major depression)	48 (18.3)	10 (16.9)	
Others (eg personality disorders and dual diagnoses)	34 (13.0)	7 (11.9)	
Re-hospitalisation in the past 3 months			
No. of re-admissions	0.40±0.29	0.49±0.31	3.38†
Length of re-hospitalisation (days)	8.12±4.11	10.01±6.38	2.16
No. of family members living with patient	2.25±0.98 (1-5)	2.13±0.98 (1-4)	1.31
Contact with main caregiver (hours/week)	30.40±9.54 (8-44)	29.13±11.49 (7-30)	1.04
Psychiatric medication			1.58
Anti-depressants	50 (19.1)	11 (18.6)	
Anti-convulsants	7 (2.7)	2 (3.4)	
Atypical anti-psychotics	90 (34.4)	19 (32.2)	
Conventional anti-psychotics	83 (31.7)	19 (32.2)	
Lithium salts	6 (2.3)	1 (1.7)	
Both anti-depressants & anti-psychotics	20 (7.6)	4 (6.8)	
Psychiatric treatments			1.48
CPN visits & education	178 (67.9)	30 (50.8)	
Family therapy/education	32 (12.2)	8 (13.6)	
Medication compliance management	102 (38.9)	16 (27.1)	
Psycho-education	98 (37.4)	28 (47.5)	
Social & work skills training	87 (33.2)	19 (32.2)	
Others (eg, relaxation & self-regulation)	75 (28.6)	20 (33.9)	
Family caregivers			
Gender			1.16
Female	158 (60.3)	34 (57.6)	
Male	104 (39.7)	25 (42.4)	
Age (years)	42.58±10.82 (21-67)	43.9±7.12	1.92
Education level			1.83
Primary or below	48 (18.3)	9 (15.3)	
Secondary	182 (69.5)	41 (69.4)	
Tertiary	32 (12.2)	9 (15.3)	
Relationship with patient			1.28
Child	38 (14.5)	8 (13.6)	
Parent	98 (37.4)	22 (37.3)	
Sibling	33 (12.6)	7 (11.8)	
Spouse	63 (24.0)	14 (23.7)	
Others (eg grand-parent and nephew)	30 (12.5)	8 (13.6)	
Household income, monthly (HK$)			1.67
≤5000	8 (3.1)	2 (3.4)	
5001-10 000	43 (16.4)	9 (15.3)	
10 001-20 000	103 (39.3)	23 (39.0)	
20 001-30 000	83 (31.7)	18 (30.5)	
>30 000	25 (9.5)	7 (11.9)	

* Data are presented as No. (%) or mean±SD (range)
† P<0.05

total scale and 0.81-0.92 for the four subscales.[4] Very minor amendments were made to the key wording of a few items. Test-retest reliability coefficient for the Chinese version over the 2-week interval was *r*=0.92 for total scale (P=0.01) and 0.89-0.95 for subscales (P=0.01-0.008), indicating a high stability of responses to the items over 2 weeks.

Phase 2

A total of 262 pairs of patients and family caregivers completed all the questionnaires (response rate, 82.0%). 59 pairs refused to participate mainly due to lack of interest or time; five questionnaires were incomplete and excluded from data analysis. The respondents and non-respondents were comparable in most sociodemographic and clinical characteristics (P>0.30, Chi-square test or independent sample *t* test, Table 1).

Construct validity

All corrected item-total correlations were positive with nearly all 52 items falling within the range of 0.30-0.70. After confirmation of its factorability, the principal components analysis and Catell's scree test indicated that there were four components (intrusiveness/hostility, attitude towards patient, tolerance, and emotional involvement) with an eigen value of >1.0, with 50 of 52 items having factor loadings of ≥0.40. Two items with very low factor loading were deleted from item rotation ("Doesn't ask a lot of personal questions" [0.17] and "Expects the same level of effort from me, even if I don't feel well" [0.19]). After varimax rotation (Table 2), all 50 items had substantial loading (≥0.40) on only one factor, except for "Can cope well with stress" (item 46) that was only counted in emotional involvement by interpreting its meaning and a higher loading. The four-factor solution (intrusiveness/hostility [12 items], attitude towards patient [13 items], tolerance [12 items]; and emotional involvement [13 items]), explained 71.8% of the total variance of EE construct.

For confirmatory factor analysis, three models were tested using LISREL 9.1, including the two-factor model suggested by the original authors, the three-factor structure suggested by Gerlsma and Hale,[1] and the four-factor model in the present study. The summary of the fit indices of the three hypothesised models with both uncorrelated and correlated factors is shown in Table 3. The four-factor model with paths between all factors showed a much better fit based on all fit indices (χ^2/df=1.93, P=0.75; AGFI=0.96; TLI=1.02; RMSEA=0.031; WRMR=0.78) than the other two models tested; and critical ratios for the regression weights were >2.0, indicating each item with a significant contribution at the 0.05 level to its associated factor. A path diagram of the best-fit four-factor model indicated

TABLE 2. Results of varimax rotation of four identified factors for the Chinese Version of the Level of the Expressed Emotion scale

Items	Factor loading ≥0.40			
	Factor 1 (intrusiveness/ hostility)	Factor 2 (attitude towards patient)	Factor 3 (tolerance)	Factor 4 (emotional involvement)
1. Doesn't butt into my conversations (3)	0.49			
2. Isn't overprotective with me (6)	0.47			
3. Doesn't insist on doing things with me (14)	0.48			
4. Doesn't pry into my life (41)	0.47			
5. Supports me when I need it (36)	0.56			
6. Isn't always interfering (10)	0.46			
7. Leaves me feeling overwhelmed (20)	0.49			
8. Often checks up me to see what I'm doing (24)	0.46			
9. Isn't always nosing into my business (28)	0.51			
10. Always has to know everything about me (32)	0.49			
11. Butts into my private matters (37)	0.45			
12. Gets upset when I don't check in with him/her (49)	0.52			
1. Is sympathetic toward me when I'm ill or upset (8)		0.51		
2. Encourages me to seek outside help when I'm not feeling well (12)		0.48		
3. Makes me feel valuable as a person (19)		0.50		
4. Tries to make me feel better when I'm upset or ill (26)		0.50		
5. Is willing to gain more information to understand my condition when I'm not feeling well (39)		0.42		
6. Doesn't blame me when I'm feeling unwell (43)		0.47		
7. Tries to reassure me when I'm not feeling well (51)		0.41		
8. Says I just want attention when I say I'm not well (4)		0.45		
9. Doesn't help me when I'm upset or feeling unwell (15)		0.47		
10. Says I cause my troubles to occur in order to get back at him/her (22)		0.50		
11. Says it is OK to seek professional help (30)		0.45		
12. Accuses me of exaggerating when I say I'm unwell (34)		0.50		
13. Often accuses me of making things up when I'm not feeling well (47)		0.48		
1. Is tolerant with me even when I'm not meeting his/her expectations (2)			0.45	
2. Can see my point of view (9)			0.41	
3. Doesn't feel that I'm causing him/her a lot of trouble (13)			0.43	
4. Understands my limitations (23)			0.46	
5. Blames me for things not going well (18)			0.51	
6. Is realistic about what I can and cannot do (27)			0.49	
7. Is understanding if I make mistakes (40)			0.42	
8. Makes me feel guilty for not meeting his/her expectations (5)			0.41	
9. Puts me down if I don't live up to his/her expectations (16)			0.40	
10. Gets angry with me when things don't go right (31)			0.42	
11. Is impatient with me when I'm not well (42)			0.42	
12. Hears me out (29)			0.43	
1. Calms me down when I'm upsets (1)				0.41
2. Doesn't panic when things start going wrong (11)				0.40
3. Is able to be in control in stressful situations (25)				0.43
4. 'Flies off the handle' when I don't do something well (48)				0.42
5. Makes me feel relaxed when he/she is around (33)				0.41
6. Can cope well with stress (38)			0.40	0.45
7. Loses his/her temper when I'm ill or upset (7)				0.41
8. Doesn't insist on being with me all the time (17)				0.41
9. Doesn't know how to handle my feelings when I'm not feeling well (21)				0.45
10. Gets angry with me for no reason (35)				0.42
11. Expects too much from me (44)				0.43
12. Makes matters worse when things aren't going well (46)				0.41
13. Gets irritated when things don't go right (50)				0.43
% of variance explained	**21.48**	**19.32**	**16.01**	**14.98**

TABLE 3. Summary of fit indices of three hypothesised models of the Level of Expressed Emotion scale (n=262)*

Model	χ^2	df	χ^2/df	P value	GFI	AGFI	TLI	RMSEA (90%CI)	SRMR	WRMR
Four-factor model										
Uncorrelated factors	98.34	50	1.97	0.80	0.97	0.96	1.00	0.040 (0.036-0.044)	0.039	0.85
Correlated factors†	92.58	48	1.93	0.75	0.99	0.98	1.02	0.031 (0.027-0.035)	0.028	0.78
Two-factor model										
Uncorrelated factors	102.33	50	2.05	0.54	0.88	0.87	0.89	0.052 (0.044-0.060)	0.050	0.92
Correlated factors	97.02	48	2.02	0.58	0.89	0.90	0.95	0.050 (0.042-0.058)	0.054	0.89
Three-factor model										
Uncorrelated factors	134.21	50	2.68	0.20	0.86	0.85	0.89	0.071 (0.061-0.081)	0.071	0.99
Correlated factors	125.88	48	2.60	0.25	0.89	0.88	0.91	0.067 (0.055-0.076)	0.060	0.94

* χ^2 denotes Chi-squared goodness-of-fit, df degree of freedom, P value (a good fit if P≥0.1), GFI goodness-of-fit index (range, 0-1, a good fit if GFI ≥0.9), AGFI adjusted good-of-fit index (a good fit if AGFI ≥0.9), TLI Tucker-Lewis index (acceptable, 0.90-0.95; a good fit if TLI >0.95), RMSEA root mean square error of approximation (a good fit if RMSEA ≤0.05), SRMR standardised root mean square residual (a good fit if SRMR <0.05), WRMR weighted root mean residual (a good fit if WRMR <0.90)

† Model fit indices tested with paths (correlations) set up between the hypothesised factors in each model

moderate correlations between four factors (0.49-0.59) and their corresponding items (0.49-0.71).

Internal consistency and concurrent validity

The internal consistency of the Chinese version of the LEE scale was high, with Cronbach's alpha of 0.90 for overall scale and 0.86-0.92 for four subscales. All corrected item-total correlations were positive (0.30-0.70). As expected, the Chinese version and its four factors negatively correlated with the FAD (r= -0.46, P<0.05 to r= -0.54, P<0.01) and its subscales (r= -0.46, P<0.05 to r= -0.68, P<0.001), and positively correlated with the FBIS (r=0.48, P<0.05 to r=0.56, P<0.01). The total and subscales of the Chinese version were also positively inter-correlated (r=0.49 to r=0.65, P<0.01).

Reproducibility and responsiveness to change of the Chinese version

Reproducibility of the Chinese version of the LEE scale between the two measurements (over a 6-month interval) in patients (n=100) who reported no major changes in either symptom severity (stable mental state) or family functioning were very satisfactory (intraclass correlation coefficient=0.90; F=5.33, df=98, P=0.01). For assessing responsiveness to changes in symptom severity, the observed changes in mean LEE score among the patients with a considerable negative change in symptom severity (n=95) ranged from 1.24 to 6.58 for overall score, and from 0.31 to 2.89 for the four subscales. The changes in the mean LEE score correlated with the pattern of changes in the severity of psychotic (r=0.57, P=0.01) or depressive (r=0.52, P=0.03) symptoms. The Chinese version showed moderate effect size (0.54) for detecting an increase in the patients' symptom severity (n=95) in the overall score and small-to-moderate effect size (0.38-0.58) in the four subscales. The Chinese version also showed moderate effect size (0.50) for detecting symptom improvement (n=70) in the overall score and small-to-moderate effect size (0.38-0.58) in the four subscales. Otherwise, the effect size for detecting changes in anxiety symptoms was very small (0.10-0.15) for all types of SMI.

Level of EE of family members perceived by patients with SMI

The mean total score of the Chinese version for patients with SMI in terms of their psychiatric diagnosis were (in descending order): 132.88 (SD, 20.54) for unipolar disorder, 121.47 (SD, 20.33) for psychotic disorders, 119.45 (SD, 23.65) for schizophrenia, and 111.01 (SD, 18.15) for bipolar disorder. The ANOVA test followed by Tukey's HSD comparisons indicated that the level of perceived EE was higher in patients with unipolar disorder than in those with schizophrenia, psychotic disorders, or bipolar disorder (P<0.01), and was higher in those with schizophrenia or psychotic disorders than in those with bipolar disorder (P<0.03 and P<0.01, respectively). For the subscales, the mean scores were higher in patients with unipolar disorder than in those with bipolar disorder (P<0.01); scores in two subscales (intrusiveness/hostility and emotional involvement) were also higher in patients with schizophrenia or psychotic disorders than in those with bipolar disorder (P<0.01).

Discussion

The Chinese version of the LEE scale demonstrated very satisfactory psychometric properties when used as a measurement of the level of EE of family

members perceived by 262 Hong Kong Chinese patients with SMI. The satisfactory weighted kappas and intraclass correlation coefficients indicated that the items in the Chinese version were appropriately translated and retained a comparable meaning to the original English version. The high test-retest reliability, internal consistency, and reproducibility also confirmed that the translated version has a high potential for application.[4,5] The association between family functioning (negative) and caregiving burden (positive) may reveal not only the good concurrent validity between these instruments but also the high impact of patients' perceived EE on family member's health and well-being in caring for a relative with SMI.[1,4] Effective strategies to reduce patients' perceived EE may also help improve family interpersonal relationships as well as family harmony and functioning, and in turn facilitate family caregivers to cope more effectively with problems and difficulties in caring for both the patient and the whole family.

The Chinese version also indicated a very satisfactory responsiveness to changes in symptom severity (depressive and psychotic symptoms) of all people with SMI, with moderate effect size for detecting both symptom deterioration and improvement over 6 months. The LEE scale may be useful to detect early relapse in schizophrenia and other SMIs, as supported by previous research in which both family- and patient-perceived EE were predictors of relapse of SMI.[6] The LEE scale also indicated moderate effect size for detecting symptom improvement in patients with SMI, particularly for the subscale emotional involvement (effect size=0.58). Emotional over-involvement in which a high level of family members' responses to a patient's daily behaviours and life activities, and sometimes his/her private matters, may impose a negative impact on the patient's psychosocial health and result in increased anxiety, self-blame, or social withdrawal.[1] Less emotional involvement by family members can result in better family functioning and better social adjustment in patients with SMI and, subsequently, less aggressive and demanding behaviour.[2] Although controversies persist about whether EE can alter the effect of family-focused intervention on mood disorders, higher EE families (especially those with higher critical comments and emotional over-involvement) report higher levels of depression over 2 years, regardless of the mode of treatment received.[6]

Some aspects of high EE, particularly the moderate level of criticisms and emotional reactions towards patient, are positively associated with better social functioning and adjustment in people with schizophrenia.[2] With an appropriate level of EE, family caregivers can exert more control over a patient's difficult behaviour and thus can better plan and monitor family activities and be more able to adjust to or cope with their caregiving role.[5]

In the present study, the hypothesised four-factor structure of the Chinese version of the LEE scale with paths (and moderate correlations) between four factors was confirmed. This four-factor model, similar to the one used in Chinese people with schizophrenia,[4] showed that intrusiveness and hostility, various negative attitudes towards the patient, level of tolerance, and extent of emotional involvement are four moderately correlated factors or concepts that cover patients' perceived EE of their family. This Chinese version is shortened (from 60 to 50 items) and can explain more variance and is more convenient and user-friendly, with higher construct validity than the original English and other versions. Intrusiveness/hostility and emotional over-involvement are the two key components of EE most commonly accepted and agreed by researchers across cultures.[2,6] The other two factors (attitudes towards patient and tolerance) have been increasingly recognised.[2] This perception is also consistent with the Chinese belief that open expression of emotions and comments, either positive or negative, should be discouraged, and self-control of emotions and negative remarks should be emphasised.[4,6] Family members with high EE have negative impact on patient's behaviour; they often expect the patient to take main responsibility for and be able to control his/her emotions and illness-related behaviours.[2] The findings of the four-factor structure provide further support for the proposed multi-dimensional nature of the family attitude and emotional environment in caring for a patient with SMI, as suggested by other studies.[1,2,4]

Participants with different types of SMI reported a moderate level of perceived EE. Consistent with other studies,[1,2] depressed patients indicated a high level of perceived EE, mainly relating to their high perceived intrusiveness and irritability (emotion over-involvement) and inadequate social support obtained from their family members. The development and course of depression is a dynamic interactional process in which family support and caring attitude can serve as a buffer to onset of the illness or a mediator of the recovery process.

The level of EE in the present study was inconsistent to that in other studies in Asian and western countries. One study reported a low level of EE in most (45-75%) families in Asian and western countries.[7] In contrast, most of our Chinese patients reported a moderate-to-high level of perceived EE. The mean EE level of our patients was higher than that of 26 depressed outpatients measured by the Dutch version of the LEE scale.[1] Our study was consistent with a study of Chinese populations in which over 40% of family members of patients with schizophrenia were rated as having high EE.[5]

Attitude and emotional responses to a mentally ill relative such as protection, hostility, anger and devotion may vary according to family dynamics and practices within a particular culture.[7] This highlights the uniqueness in Chinese culture of some (patients' perceived) family's emotional responses to their mentally ill relative. The interpretation of the dimension and degree of EE may require the inclusion of different cultures in order to be valid and accurate.

A few limitations of this study are noted. First, this study used only the patient's perception of the family member's level of EE. It is possible that the responses/ratings from the patients with SMI are unreliable due to the illness; and the correlations of LEE with other psychosocial and mental health measures would be artificially inflated. Researchers need to ensure a high level of reliability of patient's self-report by checking their mental stability and competence. Second, the sample was non-representative. Most participants were male, well-educated, Hong Kong born Chinese, mentally stable, with a primary diagnosis of one type of SMI and no co-morbidity of any other mental illnesses. The participants were recruited from one psychiatric outpatient clinic in Hong Kong, where similar socio-economic backgrounds and mental healthcare services were found. In addition, the sample size was relatively small and minimum for factor analysis of a 52-item scale. This study should be replicated in other kinds of mentally ill patients with diverse socio-demographic and clinical backgrounds. Third, the findings did not show clearly how the Chinese version of the LEE scale could be related to the original EE concept, which is operationally defined to measure the family's emotional climate and stress environment from the perspective of family caregivers. Re-examining the convergent validity of the Chinese version of the LEE scale with standard measures such as the CFI may confirm its consistency with the EE perceived by family members.

Conclusion

The Chinese version of the LEE scale is reliable and valid for measuring the level of EE of family members perceived by patients with SMI. The Chinese version showed moderate effect size for detecting changes in symptom severity in psychotic and unipolar disorders; the four-factor structure accounted for a high percentage of the total variance of the EE construct. Most patients with SMI, especially those with unipolar disorder, reported a moderate level of perceived EE. The Chinese version of the LEE scale can be further tested in healthy individuals and the general public, as well as in different Chinese communities.

Acknowledgements

This study was supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (#09101481). We thank staff in the psychiatric outpatient clinic of the mental hospital for assisting recruitment, as well as to all participated patients and their family caregivers.

References

1. Gerlsma C, Hale WW 3rd. Predictive power and construct validity of the Level of Expressed Emotion (LEE) scale. Depressed out-patients and couples from the general community. Br J Psychiatry 1997;170:520-5.
2. Butzlaff RL, Hooley JM. Expressed emotion and psychiatric relapse: a meta-analysis. Arch Gen Psychiatry 1998;55:547-52.
3. Cole JD, Kazarian SS. The Level of Expressed Emotion Scale: a new measure of expressed emotion. J Clin Psychol 1988;44:392-7.
4. Chien WT, Chan SW. Testing the psychometric properties of a Chinese version of the Level of Expressed Emotion Scale. Res Nurs Health 2009;32:59-70.
5. Li Z, Arthur D. A study of three measures of expressed emotion in a sample of Chinese families of a person with schizophrenia. J Psychiatr Ment Health Nurs 2005;12:431-8.
6. Kim EY, Miklowitz DJ. Expressed emotion as a predictor of outcome among bipolar patients undergoing family therapy. J Affect Disord 2004;82:343-52.
7. Ikram A, Suhail K, Jafery SZ, Singh S. Rates of expressed emotion in Pakistani relatives of patients with schizophrenia. Isr J Psychiatry Relat Sci 2011;48:74-81.

Mindfulness-based cognitive therapy for generalised anxiety disorder and health service utilisation among Chinese patients in primary care: a randomised, controlled trial

SYS Wong *, WK Tang, SW Mercer, K Kung, WWS Mak, SM Griffiths, TMC Lee

KEY MESSAGES

1. Both mindfulness-based cognitive therapy and psycho-education appear to reduce anxiety symptoms in patients with generalised anxiety disorder.
2. Psycho-education may be a better intervention, especially for depressive symptoms and mental health–related quality of life.

Hong Kong Med J 2016;22(Suppl 6):S35-6
HHSRF project number: 07080451

[1] SYS Wong, [2] WK Tang, [3] SW Mercer, [1] K Kung, [4] WWS Mak, [1] SM Griffiths, [5] TMC Lee

[1] *The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong*
[2] *Department of Psychiatry, The Chinese University of Hong Kong*
[3] *Institute of Health and Wellbeing, The University of Glasgow, UK*
[4] *Department of Psychology, The Chinese University of Hong Kong*
[5] *Department of Psychology, The University of Hong Kong*

* Principal applicant and corresponding author: yeungshanwong@cuhk.edu.hk

Generalised anxiety disorder (GAD) is one of the most common mental health problems in the primary care or community setting.[1] Medication or cognitive behavioural therapy is the first-line treatment for GAD, but medication is associated with side-effects and costs, and individual cognitive behavioural therapy is expensive and time-consuming. Mindfulness-based cognitive therapy (MBCT) is useful to reduce anxiety symptoms by training present-moment mindful awareness.[2] This study was conducted to compare the effectiveness of MBCT with psycho-education (based on cognitive behavioural therapy principles) and usual care in patients with GAD.[3]

A total of 182 participants aged 21 to 65 years with a principal diagnosis of GAD were randomised to receive 8 weeks of MBCT (n=61), psycho-education (n=61), or usual care (n=60). The MBCT and psycho-education groups were comparable in terms of the course structure and the therapist's contact time and attention. Participants who received usual care had unrestricted access to medical services; they were on a waiting list for MBCT and did not receive any intervention until the end of their study period (3 months after intervention). Validated scales were used to assess psychological symptoms including anxiety, worry, and depressive symptoms, and quality of care at baseline, end of intervention, and 3 months after the intervention. Participants in the MBCT and psycho-education groups were further assessed at 6 and 9 months after intervention.

At baseline, the three groups were comparable in terms of demographic and socio-economic factors as well as outcome measures. Immediately and 3 months after intervention, both MBCT and psycho-education groups demonstrated a significant reduction in anxiety score, compared with the usual care group. Anxiety score in the MBCT and psycho-education groups was comparable at any follow-up. For worry score, significant relative change was noted between the psycho-education and usual care groups at 3 months after intervention only. Significant improvement over time was noted in the psycho-education group for depressive symptoms and mental components of the health-related quality of life scale, compared with the usual care group. Nonetheless, there was no significant difference between the MBCT and usual care groups or between the MBCT and psycho-education groups. At 6 and 9 months after intervention, both MBCT and psycho-education groups showed significant improvement in outcome measures, but the two groups did not differ significantly.

Both MBCT and psycho-education were better than usual care in terms of reduced anxiety symptoms among patients with GAD. Psycho-education may have additional beneficial effects of improving worry, depressive symptoms, and mental health–related quality of life. Further studies are needed to explore whether any patient characteristics or populations are more suitable for MBCT or psycho-education. Studies of patients with recurrent depression show that those with ≥3 episodes of depression benefit most from MBCT.

Acknowledgements

This study was supported by the Health and Health

Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (#07080451). We thank the instructors who helped lead the MBCT and PE groups and those who participated.

Results of this study have been published in: Wong SY, Yip BH, Mak WW, et al. Mindfulness-based cognitive therapy v. group psychoeducation for people with generalised anxiety disorder: randomised controlled trial. Br J Psychiatry 2016;209:68-75.

References

1. Nisenson LG, Pepper CM, Schwenk TL, Coyne JC. The nature and prevalence of anxiety disorders in primary care. Gen Hosp Psychiatr 1998;20:21-8.
2. Kabat-Zinn J. Full catastrophe living: using the wisdom of your body and mind to face stress, pain, and illness. New York: Delacourt; 1990.
3. Wong SY, Yip BH, Mak WW, et al. Mindfulness-based cognitive therapy v. group psychoeducation for people with generalised anxiety disorder: randomised controlled trial. Br J Psychiatry 2016;209:68-75.

Physical health and lifestyle predictors for significant cognitive impairment in community-dwelling Chinese older adults in Hong Kong

ATC Lee, WC Chan, HFK Chiu, M Richards, LYF Hui, SPS Ng, WM Chan, LCW Lam *

KEY MESSAGES

1. The 6-year incidence of significant cognitive impairment (SCI) in community-living Chinese older people in Hong Kong is 8.6%.
2. Old age, female gender, and low educational level are risk factors for SCI.
3. Physical illnesses such as hypertension, diabetes mellitus, heart disease, and atherosclerosis are risk factors for SCI; early detection and adequate treatment of these illnesses might help reduce the risk of SCI development in older people.
4. Depression is also a risk factor for SCI.
5. Endurance exercises, stretching exercises, and mental activities are protective against development of SCI.

Hong Kong Med J 2016;22(Suppl 6):S37-9
HHSRF project number: 09100071

[1] ATC Lee, [2] WC Chan, [3] HFK Chiu, [4] M Richards, [5] LYF Hui, [5] SPS Ng, [5] WM Chan, [3] LCW Lam

[1] *Department of Psychiatry, Tai Po Hospital, Hong Kong*
[2] *Department of Psychiatry, The University of Hong Kong, Hong Kong*
[3] *Department of Psychiatry, The Chinese University of Hong Kong, Hong Kong*
[4] *MRC Unit for Lifelong Health and Ageing, UK*
[5] *Elderly Health Service, Department of Health, Hong Kong*

* Principal applicant and corresponding author: cwlam@cuhk.edu.hk

Background

Dementia is characterised by global cognitive decline and functional impairment in older people and is a growing problem in Hong Kong because of its ageing population.[1] No effective drug treatment is available to prevent the development or reverse the progression of dementia.[2] It is important to identify factors associated with its development. Minimising the detrimental effect of risk factors and optimising resilience factors may help prevent or postpone the onset of dementia and thus reduce functional impairment of older people as well as associated healthcare costs.

The Elderly Health Centres (EHCs) of the Department of Health provide annual physical check-up and cognitive assessment for enrolled Hong Kong residents aged ≥65 years. Data collected by these EHCs can help identify factors that may be associated with the development of significant cognitive impairment (SCI). The present study aimed to assess the association of basic physical health and lifestyle factors with the development of SCI in community-living active Chinese older people in Hong Kong.

Methods

This study was conducted from October 2011 to March 2013. Participants were those aged ≥65 years who attended an EHC from January to June 2005 for their annual health assessment. Those with SCI at baseline were excluded. The outcome measure was development of SCI in the following 6 years. SCI was defined by the presence of clinical dementia, scoring below the education-matched cut-off on the Cantonese version of the Mini-Mental State Examination,[3] or a global Clinical Dementia Rating score of 1 to 3.[4] Data were retrieved for analysis to determine which physical health and lifestyle factors at baseline were associated with development of SCI.

Results

A total of 18 298 older people attended the EHCs from January to June 2005, of whom 1604 were excluded because they had SCI at baseline. Of the 16 694 included, 13 626 had at least one re-assessment since 2008 (Fig). Overall, 1437 older people developed SCI within 6 years; the 6-year incidence of SCI was 8.6%. The incidence of SCI increased with advancing age.

Compared with those who remained cognitively stable, people with SCI were older (76 vs 73 years, P<0.001), more predominantly female (72.8% vs 62.8%, P<0.001), and had a lower educational level (37.5% vs 25.5% illiterate, P<0.001). Logistic regression analysis suggested that old age (OR=1.08, P<0.001), female gender (OR=1.44, P<0.001), and low educational attainment (OR=1.42, P<0.001) were independent risk factors for SCI (Table).

A higher proportion of people who developed SCI had pre-existing hypertension (69.0% vs 63.9%, P<0.001), diabetes mellitus (18.1% vs 14.8%, P=0.001), and heart disease (14.0% vs 11.2%, P=0.001) at

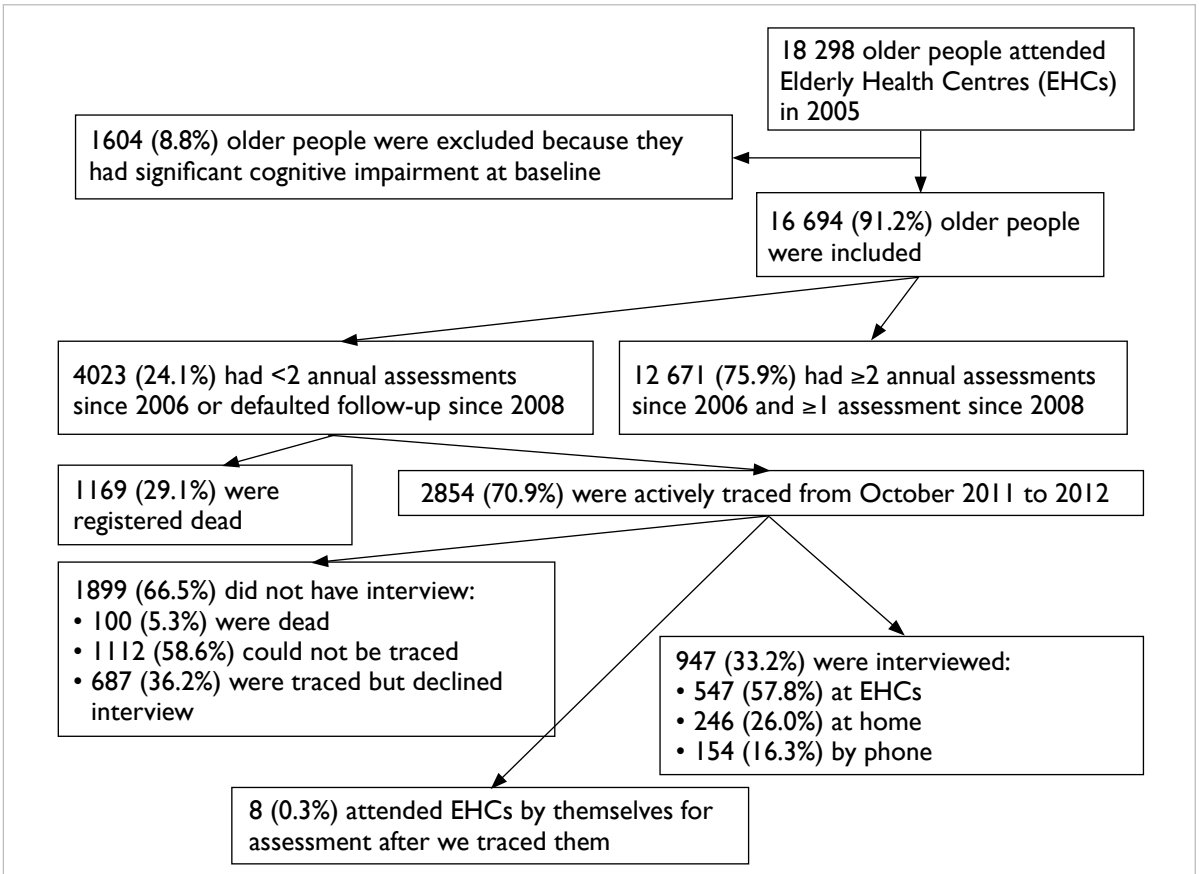


FIG. Flowchart of subject recruitment and interview

TABLE. Logistic regression analysis for risk estimate of potential factors for significant cognitive impairment

Factor	Coefficient	Standard Error	OR (95% CI)	P value
Age	0.07	0.006	1.07 (1.06-1.08)	<0.001
Female	0.23	0.07	1.26 (1.09-1.44)	0.001
Illiteracy	0.19	0.07	1.21 (1.06-1.39)	0.004
Hypertension	0.15	0.06	1.16 (1.03-1.32)	0.02
Diabetes mellitus	0.18	0.08	1.20 (1.03-1.39)	0.02
Heart diseases	0.18	0.09	1.20 (1.02-1.42)	0.03
Depression	0.13	0.14	1.14 (0.86-1.51)	0.36
15-item Geriatric Depression Scale	0.03	0.01	1.03 (1.01-1.05)	0.01
Stretching exercise	-0.28	0.11	0.75 (0.61-0.93)	0.007
Endurance exercise	-0.18	0.07	0.83 (0.73-0.95)	0.006
Adequate fruit intake	-0.09	0.06	0.91 (0.81-1.02)	0.12
Mental activities	-0.42	0.07	0.66 (0.58-0.74)	<0.001

baseline. Hypertension (OR=1.14, P=0.04), diastolic hypotension (OR=1.19, P=0.03), diabetes mellitus (OR=1.25, P=0.003), and heart disease (OR=1.24, P=0.01) were independent risk factors for SCI even after adjusting for old age, female gender, and lower educational level (Table). Optimal blood pressure control is important in reducing the risk of cognitive impairment.

People with SCI also had higher systolic blood pressure (142 vs 140 mm Hg, P=0.02), lower diastolic blood pressure (70 vs 71 mm Hg, P=0.003), and higher pulse pressure (72 vs 70 mmHg, P<0.001)

at baseline. Logistic regression analysis suggested that these were potential risk factors for SCI. As pulse pressure is an indicator of arterial stiffness, atherosclerosis might be a risk factor for SCI.

Depression was more prevalent among people with SCI (6.1% vs 3.9%, P<0.001), and logistic regression analysis suggested it to be a risk factor for SCI (OR=1.49, P=0.001, Table). Early detection and treatment of depression may help lower the risk.

Compared with those who developed SCI, a higher proportion of people who remained cognitively stable performed aerobic exercises (34.6% vs 25.4%, P<0.001), stretching exercises (11.4% vs 8.0%, P<0.001), and mental exercises such as playing Mahjong or chess (66.9% vs 50.2%, P<0.001), and had adequate fruit intake every day (ie at least two servings per day) at baseline (55.5% vs 50.4%, P<0.001). Logistic regression analysis suggested that aerobic exercises (OR=0.83, P=0.007), stretching exercises (OR=0.72, P=0.002), mental exercises (OR=0.61, P<0.001), and adequate daily fruit consumption (OR=0.86, P=0.008) were protective against the development of SCI (Table).

Conclusion

Old age, female gender, illiteracy, hypertension, diabetes mellitus, heart disease, and depressive symptoms were associated with a higher risk of SCI. Active stretching and endurance exercises and mental leisure activities were associated with a lower risk of SCI. Further studies are required to determine the underlying mechanisms of how these factors affect cognitive function and whether early detection and modulation of risk factors can improve the cognitive function of older people in Hong Kong.

Acknowledgements

This study was supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (#09100071). We would like to express our gratitude to the staff of the Elderly Health Service, the participants, and their relatives for their participation.

References

1. Census and Statistic Department. Hong Kong Population Projections 2012–2041. Hong Kong: The Government of the Hong Kong Special Administrative Region. 2012.
2. Schwarz S, Froelich L, Burns A. Pharmacological treatment of dementia. Curr Opin Psychiatry 2012;25:542-50.
3. Chiu HK, Lam LC, Chi I, et al. Prevalence of dementia in Chinese elderly in Hong Kong. Neurology 1998;50:1002-9.
4. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 1997;9(Suppl 1):173-8.

Person-centred care for demented older adults: a qualitative analysis

VWQ Lou *, GKC Law, XB Zhong

KEY MESSAGES

1. There was a lack of consensus among formal caregivers about the concept of person-centred care (PCC).
2. Formal caregivers associated PCC with positive and empathic feelings, and believed it to be in line with their professional ethics, principles, and organisational vision, mission, and values. However, ambivalent feelings were recorded when formal caregivers encountered difficulties in practising PCC. Formal caregivers reported good practices in providing daily care that aligned with PCC principles, but also admitted practices involving objectification.
3. Family caregivers and older adults with mild cognitive impairment (MCI) were unfamiliar with PCC, linking it to professional intervention. They were ambivalent about PCC, reporting feelings ranging from respect to helplessness. Family caregivers not only demonstrated elevated tendencies to infantilise older adults with MCI, but also proactively communicated with formal caregivers to achieve personalised care.
4. There should be a thorough discussion about quality dementia care standards in Hong Kong. Dementia care practices must be consolidated with reference to evidence-based interventions. Environmental context should be reviewed to identify barriers to quality care for older adults with dementia. Family caregivers and older adults with dementia should engage in the process of developing dementia care policies and practice guidelines.

Hong Kong Med J 2016;22(Suppl 6):S40-2
HHSRF project number: 09101241

[1] **VWQ Lou**, [2] **GKC Law**, [1] **XB Zhong**

The University of Hong Kong
[1] *Department of Social Work and Social Administration*
[2] *Division of Health and Applied Science, SPACE*

* Principal applicant and corresponding author: wlou@hku.hk

Introduction

The prevalence of dementia among older adults in Hong Kong has rapidly increased, with 110 000 cases in 2010 and an estimated 280 000 cases by 2036. Policymakers should adopt a scientific and efficient care model that ensures adequate quality of care for elderly individuals with dementia. Person-centred care (PCC) was developed to meet the need for patient-oriented healthcare services, based on understanding of patient circumstances and needs.[1] When caregivers apply PCC, the use of antipsychotic drugs in people with dementia is reduced as is the agitated behaviours.[2] PCC has been adopted as a standard for dementia care management in the United Kingdom, Canada, and Australia. As such, PCC is considered synonymous with good quality care for dementia patients.

This study aimed to better understand Hong Kong long-term care organisation stakeholders' attitudes towards PCC for older adults with dementia by assessing their (1) perceptions, (2) affection, and (3) practice of PCC for demented older adults, and (4) the implications for quality dementia care standards in Hong Kong.

Theoretical framework

A tripartite model of attitudes was used. This model conceptualises attitudes according to affective, behavioural, and cognitive components.[3] It is a classic theoretical approach of conceptualising attitudes. We also applied Brooker's PCC=V+I+P+S model to examine attitudes towards PCC.[4] The VIPS model has its roots in Kitwood's argument of PCC and comprises four elements: (1) V for valuing people with dementia and those who care for them, (2) I for treating people as individuals, (3) P for looking at the world from the perspective of the person with dementia, and (4) S for a positive social environment in which the person living with dementia can experience relative well-being.[4] The VIPS model has been applied to design training programmes for PCC planning and practice guidelines.[5] The present study integrated the tripartite model of attitudes and the VIPS model to investigate Hong Kong long-term care organisation stakeholders' attitudes towards PCC for older adults with dementia (Fig).

Methods

This study was conducted from October 2011 to September 2012. Qualitative research methods (focus groups and in-depth interviews) were used. Participants were recruited using purposeful sampling methods from non-governmental organisations that provide services for older adults

with dementia. After obtaining informed consent, a total of 53 participants were recruited to eight focus groups and eight in-depth interviews among four groups of stakeholders (older adults with mild cognitive impairment [MCI], family caregivers, healthcare workers, and healthcare professionals). After extensive discussion between researchers, guidelines for focus groups and in-depth interviews were developed, and pilot tests were conducted.

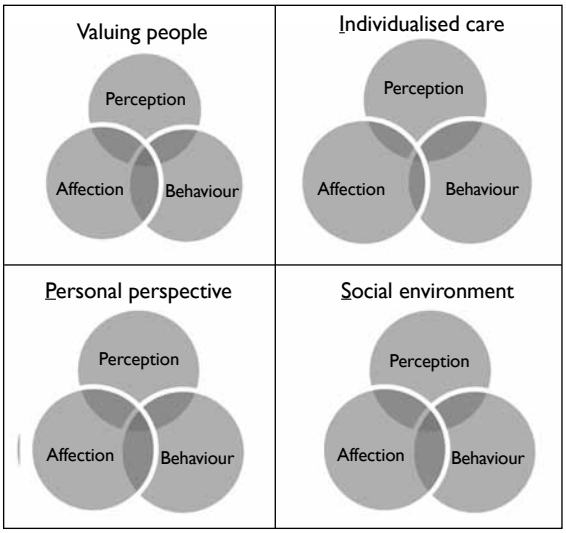


FIG. Theoretical framework

Results

The older adults with MCI (n=13) who participated in a focus group were over 70 years old and mainly female (n=11); most of them widowed (n=11) and living alone (n=7).

The family caregivers (n=16) who participated in a focus group were mainly female (n=10) and the care recipients' spouse (n=10); most had provided care for <10 years (n=14) and approximately 33% relied on the Comprehensive Social Security Assistance Scheme (n=6). The degree of social services usage varied: one carer reported never using them and three reported relying on them for 6 to 10 years; 15 reported that that the current level of social services available for older adults with dementia was insufficient.

The healthcare workers and professional staff (n=24) who participated in a focus group were mainly female (n=20) with a professional background of social work (n=6), nursing (n=3), occupational therapy (n=2), or physiotherapy (n=1).

Those who attended an in-depth interview (n=9) were female and served as unit heads (n=4), supervisors (n=3), or service managers (n=2) in residential and day- and home-care settings.

The Table summarises the major themes of formal caregivers, older adults with MCI, and family caregivers.

Perceptions of PCC

Perceptions of PCC differed between formal

TABLE. Attitudes towards person-centred care (PCC) in formal caregivers and older adults with mild cognitive impairment and family caregivers

VIPS model	Tripartite model of attitudes (perceptions, affection, and practice of person-centred care	
	Formal caregivers	**Older adults with mild cognitive impairment and family caregivers**
Valuing people	- Respect dignity is the core (perceptions) - Positive, agreeable and sympathetic (affection) - Showing courtesy and respect vs objectification, disempowerment, and infantilisation (practice)	- Unable to articulate but positive (perceptions) - Unfamiliar (affection) - Tendency to infantilisation, and high expectations of early, targeted interventions from professionals (practice)
Individualised care	- In line with holistic care approach (perceptions) - Positive and useful vs. frustration (affection) - Developing and implementing individual care plan according to comprehensive personal background information and continuous assessment (practice)	- Sensible and flexible to individual needs in cognitive training and self-care competence enhancement (perceptions) - Disappointed, impossible, and helpless (affection) - Higher expectations of cognitive/well-being interventions by professional staff (practice)
Personal perspective	- As a pathway of designing and implementing individual care plan (perceptions) - Empathy vs frustration (affection) - Comprehensive assessment, communication, and continuous observation (practice)	- Dependent on manpower and setting (perceptions) - Proactive is better (affection) - Professional knowledge and skills help (practice)
Social environment	- Help to improve patients' quality of life and as a facilitator to enforce PCC (perceptions) - Encouraging vs powerlessness (affection) - Safe and easy physical environment, positive and supportive social environment, including a variety of dementia intervention projects and activities (practice)	- Continuum of care and affordability are core (perceptions) - Ambivalent (affection) - Opt for subvented services even through it might lack manpower since self-financed services are unaffordable (practice)

caregivers and older adults with dementia and family caregivers. In general, formal caregivers recognised that PCC was concordant with their professional ethics and values, a holistic approach to individualised care that respected the dignity of older adults (by taking a personal perspective), and their principles of service delivery (but hindered by practical barriers). In contrast, older adults with MCI and family caregivers reported that they were largely unfamiliar with PCC; they were unable to articulate PCC values and principles, and only evidenced recognition of individualised care tailored to individual older adults with dementia.

Affection for PCC

Formal caregivers shared positive and affirmative affection for PCC, whereas family caregivers and older adults with MCI expressed ambivalent feelings. In general, formal caregivers affiliated PCC with positive affection; either because the values and principles of PCC were aligned with their personal values or passions, or because they expressed compassion related to the opportunity to take care of such older adults. Nonetheless, formal caregivers did feel frustrated about the environmental constraints associated with the institutional or organisational establishment. In contrast, older adults with MCI and family caregivers were disappointed with current practices of individualised care and ambivalence towards the social environment.

Practice of PCC

Formal caregivers demonstrated practices that aligned with PCC principles and guidelines, whereas family caregivers and older adults with MCI expected professional care to be available to serve this purpose. Good practices of formal caregivers included showing courtesy and respect to older adults with dementia; recognising and facilitating older adults with dementia in order to maximise their freedom; developing individualised care plans according to comprehensive assessments; and considering personal background in the process of developing and implementing care plans. Nonetheless, formal caregivers also reported that they observed instances of objectification, disempowerment, and infantilisation in daily practice, which were mainly attributed to limited resources. Family caregivers intended to infantilise older adults with dementia who deserved 'education' by people outside of family. In addition, family caregivers and older adults with dementia expressed high expectations of professionals' capability to provide targeted and effective interventions to enhance cognitive abilities and well-being (rather than only providing daily care).

Discussion

Hong Kong long-term care organisation stakeholders' attitudes towards PCC for older adults with dementia were diverse in some ways and convergent in others. Hong Kong lacks a framework for dementia care policies and guidelines. Formal caregivers offer care based on professional ethics and guidelines, whereas family caregivers and older adults with MCI lack a reference point from which to evaluate received services. PCC aligns with patient-centred care, holistic care, and person-centred methods in medical and social work professions; formal caregivers are more likely to practice their own forms of care and emphasise different components. Attitudes towards PCC held by family caregivers and older adults with dementia reflect an authority-dependent view.

Four implications can be drawn based on the findings. First, PCC was agreed upon by long-term care organisation stakeholders and can serve as a foundation for further discussion. Second, the empowerment and engagement of family caregivers and older adults with dementia is the only way to decrease the evidenced gap between them and professionals. Third, research is needed to consolidate these practices to achieve better quality of dementia care in Hong Kong. Fourth, further studies are needed to examine these views and break down environmental and contextual barriers at the community, organisational, and family level.

Acknowledgements

This study was supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (#09101241). We thank all the participants and helpers who transcribed the interviews' verbatim: Chou Chun Cheong, Kwong Yin Wah, Tsui Man Chun, Poon Zi Kwong, Ng Ka On, Chan Ka Luk, Luk Ah Nah. We would also like to express our sincerest thanks to the non-government organisations that helped recruit participants.

References

1. Kitwood T. Dementia reconsidered: the person comes first. Buckingham: Open University Press; 1997.
2. Chenoweth L, King MT, Jeon YH, et al. Caring for Aged Dementia Care Resident Study (CADRES) of person-centred care, dementia-care mapping, and usual care in dementia: a cluster-randomised trial. Lancet Neurol 2009;8:317-25.
3. Ostrom TM. The relationship between the affective, behavioral, and cognitive components of attitude. J Exp Soc Psychol 1969;5:12-30.
4. Brooker D. What is person-centred care in dementia? Rev Clin Gerentol 2004;13:215-22.
5. Davis CB, Cornman CB, Lane MJ, Patton M. Person-centered planning training for consumer-directed care for the elderly and disabled. Care Manag J 2005;6:122-30.

Home and neighbourhood environment: association with children's physical activity and obesity-related dietary behaviour

SH Wong *, WY Huang, E Cerin, Y Gao, PC Lai, A Burnett

KEY MESSAGES

1. For children aged 8 to 12 years old, their parents still have an important influence on their obesity-related behaviour, ie physical activity and dietary habits.
2. Encouraging parents to be physically active and children to take part in outdoor play may help promote an active lifestyle and prevent obesity.
3. A neighbourhood with better aesthetic characteristics and easy access to parks may help children maintain a healthy body weight.

Hong Kong Med J 2016;22(Suppl 6):S43-7
HHSRF project number: 09100581

[1] SH Wong, [2] WY Huang, [3] E Cerin, [2] Y Gao, [4] PC Lai, [5] A Burnett

[1] *Department of Sports Science and Physical Education, Chinese University of Hong Kong*
[2] *Department of Physical Education, Hong Kong Baptist University*
[3] *Institute for Health and Ageing, Australian Catholic University*
[4] *Department of Geography, University of Hong Kong*
[5] *School of Medical and Health Sciences, Edith Cowan University*

* Principal applicant and corresponding author: hsswong@cuhk.edu.hk

Introduction

It is generally agreed that the environment rather than biology has fuelled the obesity epidemic over the past few decades. Today, children are thought to be less physically active and to consume more energy-dense foods than previous generations. This applies to many countries.

Fostering behavioural changes is challenging because there are multiple factors in the obesogenic environment that support an unhealthy lifestyle and obesity-related behaviour. The multitude of environmental influences has been well conceptualised in the social-ecological theory. Specifically for children, this theory highlights the influences of the multilevel (individual, family, school, community, sociodemographic, and physical environmental) factors. Hong Kong has a mixed culture and physical environment that may have a profound impact on health-related behaviour, although the magnitude of these influences remains unknown. More research based on the social ecological model is needed to clarify the complex nature of multiple factors that shape and influence physical activity (PA) and obesity-inducing dietary behaviour of Chinese children in Hong Kong. Furthermore, objective measures of both PA and the physical environment are warranted in future research. The purposes of this study were to examine the associations of home and the neighbourhood environment with body weight status and obesity-related behaviour among school children in Hong Kong.

Methods

Participants and procedure

This study was approved by the Research Ethics Committee of The Chinese University of Hong Kong. This cross-sectional study examined an existing cohort of children who were recruited in 2009 for the Understanding Children's Activity and Nutrition study. A total of 1265 children (54% boys) aged 8 to 12 years in grades 3 to 5 from 24 primary schools during the school year 2011-12 were examined. Anthropometric data of the children (body weight and height) were collected during physical education (PE) classes or school recess by the investigators. Meanwhile, an initialised Actigraph accelerometer and a parental-reported questionnaire (assessing PA, dietary habits and multiple correlates) were distributed to the children. Parents were instructed to complete the questionnaire at home and to return the forms to the contact teacher within one to two weeks.

Physical activity and dietary behaviours

The children were instructed to wear an ActiGraph accelerometer, which was attached to an elasticised belt worn at hip-level for 7 consecutive days. The accelerometer was only removed during swimming, showering, or sleeping. A 1-minute epoch was selected to record activity patterns. Data from children who recorded at least 10 hours per day for a minimum 3 days were considered to be valid. ActiGraph data were expressed as minutes spent at

different intensities of PA based on the age-specific cut-off counts.[1] Moderate-to-vigorous PA (MVPA) was defined as ≥3 METs. In order to minimise the effects of actual wearing time on the absolute minutes, the percentage MVPA was calculated and used in regression analyses. For all children, including those whose parents did not permit them to wear an ActiGraph, a validated questionnaire[2] was used to assess their PA. Four obesity-related dietary behaviours (high-fat foods, fruit/vegetables, snacks, and soft drink intake) of the children were reported by parents. The questions were adapted from similar measures used among Chinese and Australian youths.

Correlates of variables

Parents reported their occupation, educational attainment, and marital status as well as that of their partner (where applicable), and the number of sibling children in the same residence. Measures of perceived home and neighbourhood environment were reported by parents, including social network, safety, physical environment, availability of sports facilities and local destinations. The residential address of each child was geocoded into a pair of (X,Y) coordinates for plotting on a base map of Hong Kong. These cases were weighted by population arranged in 200m x 200m grid cells for subsequent cluster analysis using the SaTScan software. Proximal neighbourhood was defined as being within an 800 m crow-fly radius of each participant's residential address. Sixteen statistically significant clusters of cases with varying circle sizes and relative risks were identified by the spatial scan statistics. The clusters were then assessed using an environment audit tool (open public recreation spaces, presence and density of food outlets, and pedestrian infrastructure). Geographic Information System (GIS) data were assembled and managed; the variables included road density and street intersection density, nearest distance to parks and recreational facilities.

Statistics

Descriptive statistics were calculated to describe the average daily time spent in MVPA and body mass index (BMI). Independent *t*-tests were used to compare gender differences. Considering that children living within clusters were more likely to be similar, generalised linear mixed models were used to examine the associations of home and neighbourhood environment with PA, dietary behaviour, and BMI. Clusters were included as the random effects. In the first step, the fixed effects were sociodemographic confounders (age, gender, parental education attainment, marital status, and number of siblings). The individual variable was entered into separate models to predict MVPA, dietary behaviour, or BMI, adjusting for sociodemographic confounders. Variables significantly related to the outcomes were then added simultaneously into the final model. Because the units of GIS-determined variables varied widely, standardised scores were generated and used for the models.

Results

A total of 1265 children and their parents were examined; 37.8% of boys and 24.7% of girls were

TABLE 1. General characteristics of the participants

Variable	Boys		Girls	
	No. of participants	Mean±SD	No. of participants	Mean±SD
Age (years)	642	9.6±1.0	547	9.7±1.0
Body mass index (kg/m^2)*	642	18.9±3.8	547	17.9±3.2
Parental educational attainment	589	4.5±1.5	495	4.6±1.5
No. of siblings*	585	0.8±0.7	497	0.9±0.8
ActiGraph-assessed moderate-to-vigorous physical activity (MVPA) [min/day]*	369	106.1±39.1	297	86.5±32.4
Questionnaire-assessed MVPA (min/day)	569	95.5±116.5	502	104.4±115.9
Soft drink intake per day	515	0.2±0.3	440	0.2±0.2
High-fat food intake per day	515	0.3±0.4	440	0.3±0.4
Snack intake per day*	515	0.8±0.8	440	1.0±0.9
		% of participants		% of participants
Actigraph-assessed %MVPA*	369	14.3±5.1	297	11.4±4.0
Sufficient consumption of fruit (≥2 servings per day)*	515	21.0	440	26.4
Sufficient consumption of vegetables (≥3 servings per day)*	515	21.5	440	24.2

* Gender difference

classified as overweight or obese according to the age- and gender-specific criteria for childhood obesity (Table 1).[3] Parental questionnaires were obtained from 1130 (89%) children. There were no differences in basic characteristics between children who wore the accelerometer and those who did not. Among 694 children who agreed to wear the accelerometer, 297 girls and 369 boys provided valid data. Boys accumulated more minutes of accelerometer-determined MVPA than girls although there was no gender difference in parent-reported MVPA. More girls than boys had sufficient consumption of vegetables (≥3 servings per day) and fruit (≥2 servings per day). Snack intake was more obvious in girls than boys.

After controlling for age, gender, highest parental education attainment, marital status, and number of siblings, three variables were associated with objectively assessed %MVPA: parental role modelling of PA, preference for play outdoors, and attractive natural sights in the neighbourhood (Table 2). In predicting questionnaire-determined MVPA, parental role modelling of PA and social network were positively associated with parental reported minutes of a child's MVPA. Children whose parents reported a lower preference for play outdoors were less likely to participate in MVPA.

Significant variables were only found for the three dietary behaviours: vegetable consumption, soft drink and high-fat food intake (Table 2). After adjusting for the confounders, grocery diversity in the neighbourhood was negatively related to sufficient consumption of vegetables. In addition, children with parents who had more eating rules at home were less likely to consume soft drinks and high-fat foods.

The associations of the home and neighbourhood environment with obesity are shown in Table 3. Children living in a neighbourhood further away from a park and with fewer trees were more likely to be obese. Interactions were found between parental education attainment and these

TABLE 2. Associations of perceived and objectively assessed environment with moderate-to-vigorous physical activity (MVPA) and dietary behaviours*

Variable	Coefficient	SE	P value	95% CI
Actigraph-assessed MVPA (n=552)				
Gender (reference=boys)	-0.273*	0.040	0.000	-0.351, -0.194
Age	-0.166*	0.020	0.000	-0.204, -0.127
Parental role modelling for physical activity	0.046*	0.018	0.010	0.011, 0.082
Preference for outdoor play	-0.059*	0.023	0.012	-0.105, -0.013
Attractive natural sights	0.101*	0.042	0.018	0.018, 0.185
Questionnaire-determined MVPA (n=968)				
No. of siblings	-0.183*	0.056	0.001	-0.292, -0.073
Parental role modelling for physical activity	0.146*	0.039	0.000	0.069, 0.223
Social network	0.095*	0.029	0.001	0.038, 0.151
Availability of sports facilities	-0.016	0.035	0.641	-0.085, 0.053
Preference for outdoor play	-0.111*	0.045	0.014	-0.199, -0.023
Local destinations	0.021	0.014	0.150	-0.007, 0.049
Attractive buildings	0.082	0.046	0.074	-0.008, 0.173
Sufficient vegetable consumption (n=855)				
Parental education attainment (primary school or less vs tertiary level)	-0.790*	0.393	0.045	-1.564, -0.017
Marital status	-0.452*	0.226	0.047	-0.897, -0.007
Grocery diversity	-0.26*	0.118	0.028	-0.492, -0.028
Eating rules at home	0.168	0.110	0.129	-0.049, 0.384
Soft drink (n=855)				
Parental education attainment (primary school or less vs tertiary level)	0.311*	0.136	0.023	0.043, 0.579
Eating rules at home	-0.089*	0.042	0.034	-0.171, -0.007
High fat foods (n=855)				
Eating rules at home	-0.110*	0.049	0.025	-0.205, -0.014

* Generalised linear mixed models controlled for demographic factors (age, gender, marital status for parents, parental education attainment and number of sibling) and adjusted for neighbourhood clustering. Only significant factors in the bivariate model are included in the final model. For sociodemographic factors, only significant variables are shown.

TABLE 3. Associations of home and neighbourhood environment with obesity*

Variables†	Coefficient	SE	P value	95% CI
Gender (reference=boys)	-0.806*	0.338	0.018	-1.471, -0.140
Preference for outdoor play	0.291	0.152	0.055	-0.007, 0.589
Nearest network distance to park*EDU=1	-0.063	0.355	0.859	-0.761, 0.635
Nearest network distance to park*EDU=2	0.863*	0.333	0.010	0.210, 1.517
Nearest network distance to park*EDU=3	0.039	0.631	0.950	-1.200, 1.279
Presence of trees	-0.345*	0.158	0.029	-0.655, -0.035

* Generalised linear mixed models controlled for demographic factors (age, gender, marital status for parents, parental education attainment and number of sibling) and adjusted for neighbourhood clustering (n=928). Only significant factors in the bivariate model are included in the final model. For socio-demographic factors, only significant variables are shown.

† EDU 1 denotes primary education or no formal education, EDU 2 secondary education, and EDU 3 tertiary education

two environmental variables. The influence of neighbourhood variables seemed to exist only for children with less educated parents.

Discussion

The current study examined a variety of features within the home and neighbourhood environment that might influence children's PA participation, dietary behaviour, and body weight status in Hong Kong. Several potentially modifiable factors were associated with the risk of being obese, being physically inactive, and adopting unhealthy dietary habits. The findings suggest that encouraging parents to be physically active and children to take part in outdoor play may help promote an active lifestyle and prevent obesity. In addition, neighbourhoods with better aesthetic characteristics and easy access to parks may help children maintain a healthy body weight.

Social factors in the home and neighbourhood environment have been extensively examined for children in western countries. Consistent with the literature, the current study found that parental role modelling of PA was an important factor of children's MVPA. In addition, children were more likely to be physically active if they preferred outdoor play. Although the existing studies of the relationship between time spent outdoors and PA in children have been mainly cross-sectional in design, the findings suggest that children tend to be more physically active if they spend more time outdoors.[4] Certain characteristics of the neighbourhood environment, eg aesthetics, may influence an individual's willingness to spend time outdoors and thus increase opportunities to be physically active. For adults, aesthetics-PA associations have been supported by a multi-site comparison study across 11 regions including Hong Kong.[5] It may also be important for children; children living in a neighbourhood with more attractive buildings or natural sights spent more time in PA.

If parents applied more rules to their child's eating behaviour, their children were less likely to adopt unhealthy eating habits (ie, a lower intake of soft drinks and high-fat foods). Regarding the influence of the built environment on healthy food consumption, diversity of food and grocery stores rather than prevalence of these stores was related to vegetable consumption. The food environment in Hong Kong may be distinctly different to that of western countries; only 1% of children's parents reported lack of a food or grocery stores within 800 meters of their home. On the contrary, diversity may reflect the variety of items available in these stores. Many of the choices may be energy-dense or processed foods that may compete with sales of more healthy foods due to taste preferences.

There is a growing body of literature to show the relationships between perceived and built environment features and PA or dietary behaviour of children. Nonetheless, few studies have investigated the impact of the environment on obesity. We found that the aesthetics of the neighbourhood environment (presence of trees) were related to a reduced risk of being obese. In addition, interaction effects were found for socio-economic characteristics with GIS-assessed accessibility of facilities. Specifically, the likelihood of being obese was positively associated with nearest distance to a park in the neighbourhood, but only in children with parents who had completed secondary education. Previous studies of spatial accessibility of sport facilities have seldom controlled for socio-economic status. In French children, low spatial accessibility of urban PA facilities led to an increased likelihood of being overweight in blue-collar-workers' children, but not in children from higher socio-economic status families.[6] It seems that for people living in an ultra-dense environment such as Hong Kong, a

pleasant neighbourhood is an important feature, especially for children from lower educated families.

Conclusion

Both the social and physical environment in the home and neighbourhood may be important factors for obesity-related behaviour of Chinese children in Hong Kong. Strategies that encourage parents to be more physically active and children to take part in outdoor play, and provide a pleasant neighbourhood with easy access to parks are warranted in future research for developing obesity intervention programmes.

Acknowledgements

This study was supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (09100581). We thank all the participating schools, children, and parents.

References

1. Trost SG, Pate RR, Sallis JF, et al. Age and gender differences in objectively measured physical activity in youth. Med Sci Sports Exerc 2002;34:350-5.
2. Huang YJ, Wong SH, Salmon J. Reliability and validity of the modified Chinese version of the Children's Leisure Activities Study Survey (CLASS) questionnaire in assessing physical activity among Hong Kong children. Pediatr Exerc Sci 2009;21:339-53.
3. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240-3.
4. Ferreira I, van der Horst K, Wendel-Vos W, Kremers S, van Lenthe FJ, Brug J. Environmental correlates of physical activity in youth - a review and update. Obes Rev 2007;8:129-54.
5. Cerin E, Cain KL, Conway TL, et al. Neighborhood environments and objectively measured physical activity in 11 countries. Med Sci Sports Exerc 2014;46:2253-64.
6. Casey R, Chaix B, Weber C, et al. Spatial accessibility to physical activity facilities and to food outlets and overweight in French youth. Int J Obes (Lond) 2012;36:914-9.

Published by the Hong Kong Academy of Medicine Press for the Government of the Hong Kong Special Administrative Region. The opinions expressed in the *Hong Kong Medical Journal* and its supplements are those of the authors and do not reflect the official policies of the Hong Kong Academy of Medicine, the Hong Kong Medical Association, the institutions to which the authors are affiliated, or those of the publisher.