SUPPLEMENT 4

HONG KONG MEDICAL JOURNAL 香港醫學雜誌 24(S4)

HONG KONG

Volume 24 Number 4 **August 2018**

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

MEDICAL JOURNAL
香港醫學雜誌

Volume 24 Number 4 **August 2018**

Health and Health Services Research Fund
Health and Medical Research Fund

Research Dissemination Reports

衞生及醫護服務研究基金
醫療衞生研究基金

研究成果報告

Chronic disease
慢性病

Cancer
癌症

Audiology
聽覺學

Supplement 4

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 24 Number 4 **August 2018**
SUPPLEMENT 4

Health and Health Services Research Fund

Health and Medical Research Fund

Research Dissemination Reports

CHRONIC DISEASE

CANCER

AUDIOLOGY

Editorial

Dissemination reports are concise informative reports of health-related research supported by the Health and Medical Research Fund (and its predecessor funds) administered by the Food and Health Bureau. In this edition, we present 11 dissemination reports of projects related to chronic disease, cancer, and audiology. In particular, three projects are highlighted for their potentially significant findings, impact on healthcare delivery and practice, or contribution to health policy formulation in Hong Kong.

In Hong Kong, 30% of the population has a chronic health condition, the most common of which is hypertension. Almost 90% of patients with chronic diseases receive follow-up care in the public sector. Most patients with hypertension are under satisfactory control, but they still receive follow-up every 2 to 4 months for repeat prescriptions. Yip et al[1] conducted a 1-year prospective randomised two-arm intervention study involving 400 older patients receiving anti-hypertensive medicine. They found that nurse-led repeat prescription was well accepted by patients with good compliance. Clinical outcomes of nurse-led repeat prescriptions were non-inferior to doctor consultations.

Advanced age, race, and family history of prostate cancer are established risk factors of prostate cancer. The influence of environmental factors on prostate cancer aetiology remains unclear. Tse et al[2] aimed to document the association between environmental exposure to bisphenol A (BPA) and the risk of prostate cancer among Hong Kong Chinese men, and to examine the exposure-response relationship between cumulative BPA exposure index and prostate cancer risk. A positive exposure-response relationship between cumulative BPA exposure index and prostate cancer was observed, with a more prominent gradient in men under the age of 70 years. The use of commercial food containers was positively related to prostate cancer risk, but only habitual drinking of chilled water in a plastic container showed a significant association.

Tinnitus is a self-reported phenomenon not readily apparent to others. Subjective psychometric measures are used to assess the severity and impacts of tinnitus and to determine the effectiveness of intervention. The Tinnitus Functional Index (TFI) is a 25-item self-administered questionnaire that assesses eight domains of negative tinnitus impact (intrusive, sense of control, cognitive, sleep, auditory, relaxation, quality of life, and emotion) using an 11-point scale (0-10). Kam et al[3] translated the TFI into Chinese and validated its use in Hong Kong Chinese patients with chronic tinnitus. Its psychometric properties (reliability, construct validity, and responsiveness) were determined. They found that the Chinese version TFI was valid and reliable for measuring tinnitus severity and related negative impacts in Chinese patients.

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 (https://rfs2.fhb.gov.hk/). 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. Yip BH, Lee EK, Sit RW, et al. Nurse-led repeat prescription for patients with controlled hypertension: a randomised controlled trial. Hong Kong Med J 2018;24(Suppl 4):S4-7.
2. Tse LA, Ho WM, Wang F, He YH, Ng CF. Environmental risk factors of prostate cancer: a case-control study. Hong Kong Med J 2018;24(Suppl 4):S30-3.
3. Kam AC, Leung EK, Chan PY, Cheung AP, Tong MC. Cross-cultural adaptation of the Tinnitus Functional Index for measurement of chronic tinnitus in Hong Kong Chinese patients. Hong Kong Med J 2018;24(Suppl 4):S42-5.

Nurse-led repeat prescription for patients with controlled hypertension: a randomised controlled trial

BHK Yip *, EKP Lee, RWS Sit, C Wong, X Li, ELY Wong, MCS Wong, RYN Chung, VCH Chung, K Kung, SYS Wong

KEY MESSAGES

1. Nurse-led repeat prescription is well accepted by patients with good compliance.
2. Clinical outcomes of nurse-led repeat prescription are non-inferior to doctor consultation.
3. Policy makers may explore and expand the role of nurses in public primary care settings.

Hong Kong Med J 2018;24(Suppl 4):S4-7
HMRF project number: 11121041

[1] **BHK Yip,** [1] **EKP Lee,** [1] **RWS Sit,** [1] **C Wong,** [1] **X Li,** [1] **ELY Wong,** [1] **MCS Wong,** [1] **RYN Chung,** [1] **VCH Chung,** [2] **K Kung,** [1] **SYS Wong**

[1] *Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong*
[2] *Private practice*

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

Introduction

Repeat prescription of medication for patients with well-controlled chronic diseases without a direct consultation does not necessarily indicate suboptimal care; one examination a year may be more effective than six short consultations with brief exchanges of courtesies.[1] In fact, repeat prescription is convenient to and welcomed by patients, as it facilitates access to medicines and utilisation of economic and human resources.[1]

In Hong Kong, 30% of the population has chronic conditions, of which hypertension is the most common.[2] More than 87% of patients with chronic diseases receive follow-up in the public sector.[2] Most patients with hypertension are under satisfactory control, but they still receive follow-up every 2 to 4 months for repeat prescription. The amount of medications dispensed per prescription is limited, thus controlling the cost per prescription. However, this comes at the expense of general outpatient clinic appointments, which could be used for patients with other problems.[3]

Methods

This was a 1-year, prospective, randomised, two-arm intervention study. Patients were recruited from Lek Yuen General Outpatient Clinics in Shatin, Hong Kong, between 28 March 2014 and 30 January 2015 by referrals from 15 primary care doctors. Informed consent was obtained from each participant. The inclusion criteria were (1) diagnosis with hypertension with systolic blood pressure (SBP) of <140 mm Hg and diastolic blood pressure (DBP) of <90 mm Hg at recruitment, (2) no medication titration in the previous 12 months, and (3) no history of cardiovascular diseases, diabetes mellitus, or hypertension complications (as per annual blood and urine checks). Patients were excluded if they were (1) unable to give consent, (2) concurrently in another clinical trial, (3) planned to become pregnant in 1 year or were pregnant at recruitment, or (4) had a known history of renal impairment or cardiovascular disease.

Participants were equally randomised into intervention and usual care groups using computer-generated random numbers. Blood pressure (BP) was measured by a clinical assistant using validated automatic BP monitoring machines. Clinical parameters were retrieved from the Hospital Authority Clinical Management System. Patients received follow-up at months 0, 4, and 8. Usual care resumed at the end of the study (month 12). Patients were encouraged to book episodic appointments for acute illnesses.

In the intervention group, repeat prescription was led by a research nurse. A protocol was developed to ensure consistency: (1) drug compliance and BP of patients were checked at every visit; (2) if BP was normal, a repeat prescription that was pre-signed by the case doctor was issued (as prescriptions can only be provided by medical doctors in Hong Kong); (3) if SBP was >140 mm Hg and/or DBP was >90 mm Hg, the BP was rechecked; (4) if the rechecked BP was between 140/90 mm Hg and 160/95 mm Hg, medication was prescribed and the follow-up was shortened to 1 month; if the patient had abnormal BP during the subsequent visit, the nurse consulted the doctor; (5) if the rechecked BP was >160/95 mm Hg, the nurse consulted the doctor within the same day; (6) the nurse could consult with the attending doctor about complications, side-effects, and concerns about the medication.

The primary outcome measures were SBP and DBP at month 12. The secondary outcome measures were the patient enablement index (which comprises

six questions with a total score of 0-12, with a higher score indicating greater enablement), patients' health service utilisation, frequency of consultations in general and special outpatient clinics, number of admissions to accident and emergency departments, number of hospitalisations, and self-reported private clinic visits.

To assess potential changes to prescriptions, five types of anti-hypertensive prescriptions were recorded at baseline and month 12: (1) angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers such as lisinopril and losartan, (2) beta-blockers such as atenolol and metoprolol, (3) calcium channel blockers such as amlodipine and nifedipine, (4) drugs containing thiazide diuretics such as indapamide, hydrochlorothiazide, and moduretic, and (5) other prescriptions such as alpha blockers or central acting agents such as methyldopa and prazosin. A score of 1 indicated a change of prescription, and 0 indicated the same prescription as the previous one.

Results

Of the 406 recruited patients, 13 were excluded because of elevated BP (n=4), diabetes (n=2), not receiving hypertension medications (n=1), lack of an annual assessment (n=1), lack of electronic records (n=1), and cognitive impairment (n=4). The remaining 393 participants were randomised to the intervention (n=194) and usual care (n=199) groups. In the intervention group, seven participants dropped out because they felt more secure seeing the case doctor (n=4) or were referred to doctors for newly diagnosed diabetes mellitus (n=1), skin problems (n=1), or hyperthyroidism (n=1). In the usual care group, seven participants were lost to follow-up. The modified intention-to-treat analysis was based on 194 and 192 patients, and the per-protocol analysis was based on 187 and 192 patients in the intervention and usual care groups, respectively (Fig 1).

The mean patient age was 63.5 years; most patients were female, married, non-smokers, had a primary to secondary education level, and about half had been diagnosed with hypertension >7 years prior (Table). Calcium blockers were the most common anti-hypertensive used, followed by beta-blockers. The two groups were comparable in terms of demographics, years since hypertension diagnosis, anti-hypertensive prescriptions, and primary and

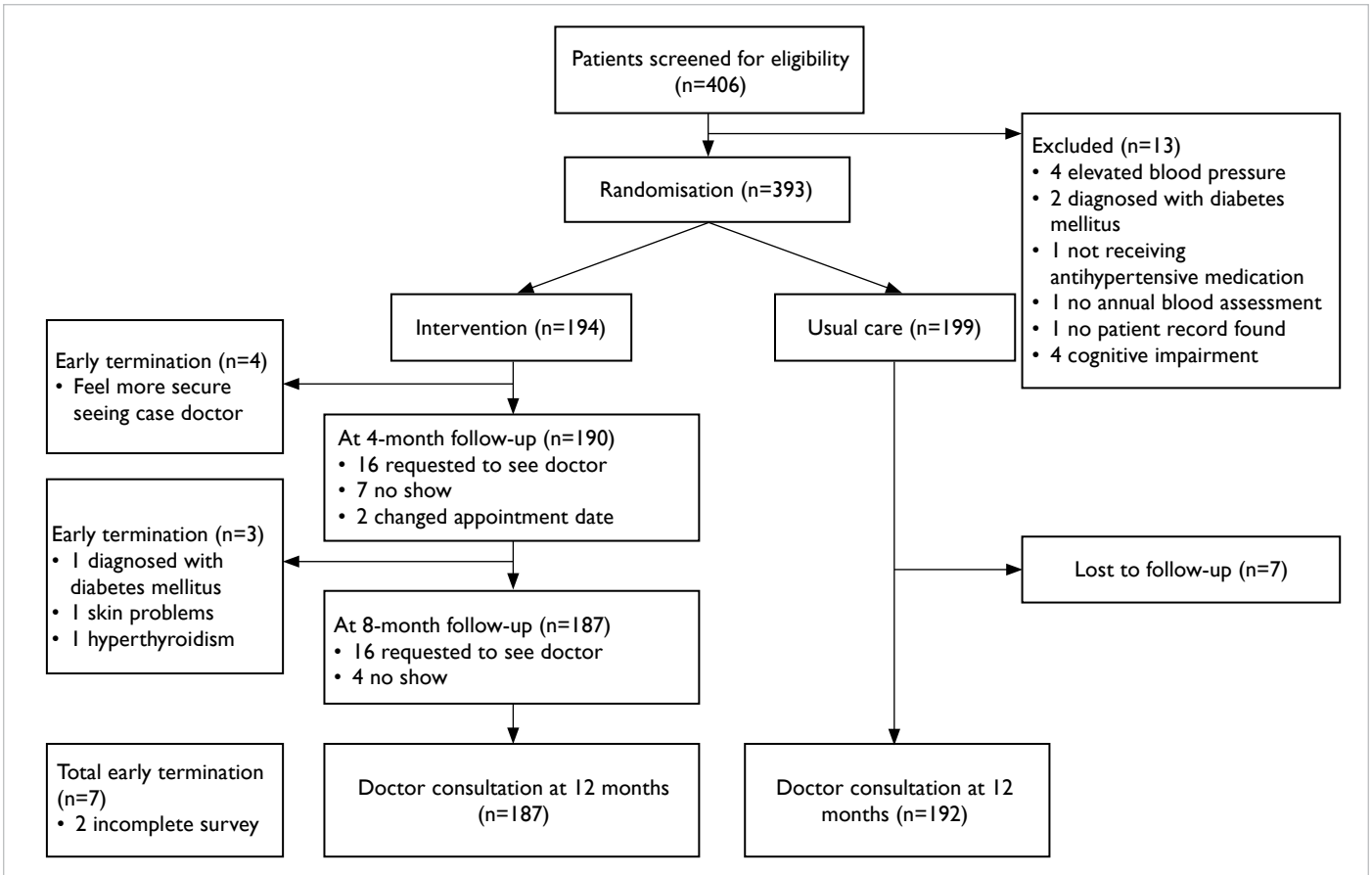


FIG 1. CONSORT flow diagram

TABLE. Participant characteristics at baseline

Variable	Usual care (n=199)*	Nurse-led repeat prescription (n=194)*	P value*
Systolic blood pressure, mm Hg	123.4±10.8	123.8±9.7	0.666
Diastolic blood pressure, mm Hg	72.3±9.0	73.1±9.4	0.429
Age, y	62.9±8.3	64.0±9.1	0.197
No. of male participants	72 (36.2)	85 (43.8)	0.149
Marital status			0.347
Single	15 (7.5)	7 (3.6)	
Married	149 (74.9)	151 (77.8)	
Widowed	24 (12.1)	22 (11.3)	
Separated	11 (5.5)	14 (7.2)	
Education level			0.330
Illiterate	21 (10.8)	21 (10.8)	
Primary 1-6	79 (40.5)	90 (46.4)	
Secondary 1-7	85 (43.6)	79 (40.7)	
Tertiary or above	10 (5.1)	4 (2.1)	
Smoking status			0.301
Current	13 (6.5)	14 (7.2)	
No	167 (83.9)	152 (78.4)	
Past	19 (9.5)	28 (14.4)	
Years since hypertension diagnosis			0.338
<2	35 (17.7)	32 (16.6)	
2-7	63 (31.8)	75 (38.9)	
>7	100 (50.5)	86 (44.6)	
Patient enablement index	3.1±2.9	2.71±2.9	0.175
Anti-hypertensive prescription			0.081
Angiotensin converting enzyme inhibitors (lisinopril) or angiotensin receptor blockers (losartan)	26 (13.1)	42 (21.6)	
Beta-blockers (atenolol, metoprolol)	68 (34.2)	56 (28.9)	
Calcium blockers (amlodipine, nifedipine)	145 (72.9)	149 (76.8)	
Diuretics (hydrochlorothiazide, moduretic)	21 (1.0)	20 (10.3)	
Others (methyldopa, prazosin)	2 (1.0)	8 (4.1)	

* Data are presented as mean±standard deviation or No. (%) of participants

secondary outcomes such as SBP, DBP, and patient enablement index.

After adjusting for baseline values, patients in the intervention group had a non-significantly higher estimated SBP (mean group difference, 0.53 mm Hg; 95% confidence interval [CI], −2.05 to 3.11 mm Hg) and DBP (mean group difference, 1.23 mm Hg; 95% CI, −0.27 to 2.73 mm Hg) than those in the usual care group at the end of the trial (Fig 2). Repeat prescription was non-inferior to usual care because the lower boundary of the 95% CI did not cross the pre-set non-inferiority margin for SBP (6.6 mm Hg) or DBP (3.7 mm Hg). The results were similar between the modified intention-to-treat analysis and the per-protocol analysis, mainly owing to high compliance to the intervention.

The patient enablement index scores at 12 months were similar in the two groups, irrespective of the type of analysis.

In terms of health care utilisation, private hospitalisation was rare (n=12), but consultations in private clinics were more common. A bimodal pattern was observed: <50% of patients did not visit private clinics, but about 36% received care in private clinics on >10 occasions in the 12 months of the study. In addition to regular visits for anti-hypertensive prescriptions (about 4-5 times annually), >27% of the patients made additional general outpatient clinic visits. About 15% of the patients visited accident and emergency departments, and similar percentage of

patients were admitted to public hospitals. Generally, there was no change (>90%) to the type and dose of anti-hypertensive prescribed. Health care utilisation and rate of change to anti-hypertensive prescriptions were comparable between groups.

Discussion

The safety of nurse-led repeat prescription was supported by the similar BP outcomes observed, lack of dropout from the intervention group, lack of adverse events, similar medication change in both groups, and similar rates of seeking alternate sources of medical attention. Nurse-led repeat prescription seems to be acceptable by patients; only four patients opted for assessment by their case doctors. Similar observations have been previously reported.[4] Patients believe that repeat prescription may reduce doctors' workload.[5] Patients also reported receiving longer consultations, more information about their condition, and medication information from the repeat prescription pharmacist.[5]

For repeat prescription to be implemented widely in primary care, a system with good communication is needed. Similar programmes involving doctors, nurses, and pharmacists were introduced in the UK in 2003.[5] Although nurses and pharmacists generally have increased job satisfaction,[5] they are concerned about professional consequences of any errors, risks to patient safety, legal considerations, lack of competency, and lack of definition of their role in patients' care.[4] There is a need for continuing education for nurses and pharmacists who participate in the programme.[5] In addition, doctors might be professionally defensive about the erosion of doctors' traditional roles, professional hierarchies, and safety.[5]

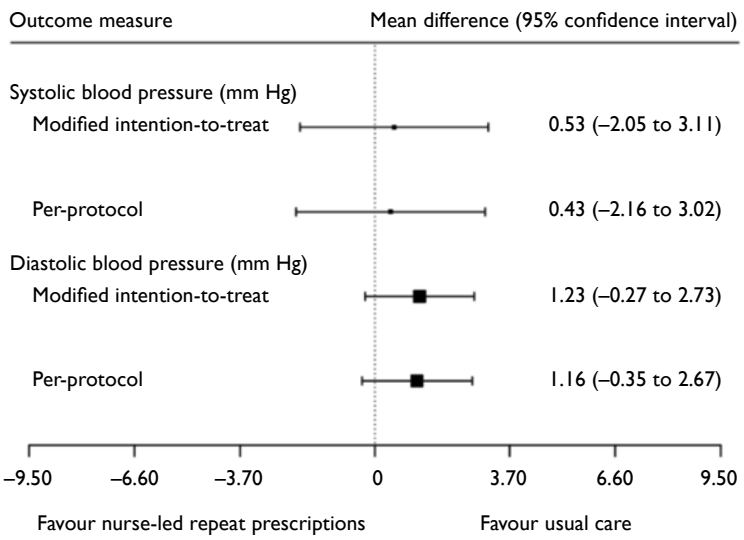


FIG 2. Estimated mean difference between systolic blood pressure and diastolic blood pressure

Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#11121041). We would like to thank all of the participants and students. We would like to express our sincere gratitude to the participating nurses and doctors, especially Dr Li Heung-wing from Lek Yuen General Out-Patient Clinic, for facilitating recruitment and referral of patients.

References

1. Drury VW. Repeat prescribing - a review. J R Coll Gen Pract 1982;32:42-5.
2. Census and Statistic Department of Hong Kong Special Administrative Region. Thematic household survey report 58. Available from: https://www.statistics.gov.hk/pub/B11302582015XXXXB0100.pdf. Accessed 10 January 2017.
3. Legislative Council. Meeting minutes. Available from: http://www.legco.gov.hk/yr04-05/english/counmtg/minutes/cm050706.pdf. Accessed 9 Mar 2017.
4. Maddox C, Halsall D, Hall J, Tully MP. Factors influencing nurse and pharmacist willingness to take or not take responsibility for non-medical prescribing. Res Social Adm Pharm 2016;12:41-55.
5. Cooper RJ, Anderson C, Avery T, et al. Nurse and pharmacist supplementary prescribing in the UK: a thematic review of the literature. Health Policy 2008;85:277-92.

Framingham risk score for predicting cardiovascular disease in older adults in Hong Kong

JYY Leung *, SL Lin, RSY Lee, TH Lam, CM Schooling

KEY MESSAGES

1. The Framingham risk score, a widely used cardiovascular disease (CVD) risk prediction tool, overestimated the risk in a large cohort of older Chinese adults in Hong Kong despite recalibration. It should be used with caution for this population.
2. Our study was limited by the lack of comprehensive laboratory predictors and CVD incidence data. New risk prediction models should be developed for specific settings with CVD incidence data.

Hong Kong Med J 2018;24(Suppl 4):S8-11
HMRF project number: 12133051

[1] JYY Leung, [1] SL Lin, [2] RSY Lee, [1] TH Lam, [1,3] CM Schooling

[1] *School of Public Health, The University of Hong Kong, Hong Kong*
[2] *Elderly Health Service, Department of Health, Hong Kong*
[3] *School of Public Health and Health Policy, City University of New York, USA*

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

Introduction

Cardiovascular disease (CVD), including ischaemic heart disease and stroke, is a leading cause of death. Many clinical guidelines recommend that clinicians use risk prediction tools to identify individuals at high risk of CVD. The predicted CVD risk can then guide clinical decisions on the intensity of preventive interventions, especially the use of statins or other lipid-lowering therapies.

The Framingham risk score (FRS) is the most widely used risk prediction tool.[1] It predicts the risk of incident CVD events over the subsequent 10 years. The original FRS was derived from middle-class Caucasian individuals and has been shown to systematically overestimate the risk of CVD in other ethnic groups, including Chinese.[2,3] Patterns of CVD in the Hong Kong population differ from those in Caucasian populations, with lower incidence of ischaemic heart disease and higher incidence of haemorrhagic stroke and diabetes mellitus.[4] The Hong Kong Department of Health recommends that primary care physicians use the FRS to assess individual CVD risk but also acknowledges that the FRS probably overestimates the risk in the local population. With population ageing, CVD is more prevalent. In a prospective study of 2895 Hong Kong Chinese people aged 25 to 74 years, the FRS overestimated the CVD risk by 1.5-fold in men but was fairly accurate when applied to women.[5] Nonetheless, whether the FRS can be applied specifically to older Chinese adults in Hong Kong remains unclear. This study compared the predictive performance of the FRS, specifically a simple office-based CVD risk prediction function, directly and after recalibration, in a large cohort of Chinese older adults in Hong Kong.

Methods

This study was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster. We used data from the Department of Health Elderly Health Service cohort that included 66 820 older Chinese adults (aged ≥65 years) enrolled at elderly health centres in Hong Kong from July 1998 to December 2001 and followed up passively for >10 years until May 2012. Details of the cohort have been described in a previous study.[4] The 18 elderly health centres provide primary care services for older adults; all Hong Kong residents aged ≥65 years are encouraged to enrol in the service for a small annual fee. More women than men are enrolled; otherwise, participants were similar to the general elderly population in terms of age, socioeconomic status, current smoking status, and hospital use.[4]

At the elderly health centres, specifically trained nurses and doctors provided health assessments and physical check-ups using structured interviews and comprehensive clinical examinations. Height, weight, and blood pressure were measured according to standard protocols. Self-reports of chronic diseases were confirmed and supplemented by clinical diagnoses based on history. Serum samples were tested for total cholesterol.

The office-based FRS was derived from the following non-laboratory predictors: age, body mass index, systolic blood pressure, treatment for hypertension, smoking, and diabetes status.[1] To

ensure comparability, stratification of predictors or risk factors was based on the FRS.

Death from CVD events at 10 years of follow-up was as defined by the Framingham Heart Study. Vital status was ascertained from death registration by record linkage using Hong Kong identity card numbers. Causes of death were routinely coded by the Department of Health according to the International Classification of Disease. Fatal CVD was defined as death from ischaemic heart disease, cerebrovascular events, peripheral artery disease, intermittent claudication, or heart failure.[1] To estimate the incidence of all CVD events, a ratio of 8:1 for non-fatal to fatal events was assumed based on the number of inpatient discharges and CVD deaths in the Hospital Authority Statistical Report 2012-2013 because participants were not actively followed up at 10 years from enrolment.

Only participants aged 65 to 74 years at baseline were included. Participants with a history of CVD or missing predictors at baseline were excluded. Baseline CVD was defined as self-reported physician-diagnosed ischaemic heart disease, circulatory disease, or peripheral vascular disease.

The FRS has been reported to predict 10-year risk of CVD events based on a sex-specific Cox proportional hazards regression model on 8491 participants aged 30 to 74 years who were free from CVD at the time of examination between 1968 and 1987 and were followed up for a maximum of 12 years.[1] The algorithm used to derive the FRS has good calibration and discrimination.[1] In the present study, a simpler office-based version was used. This non-laboratory-based score uses body mass index (instead of total and high-density lipoprotein cholesterol) and thus is more suitable for resource-limited settings and primary care.[3] It has comparable performance with models that use cholesterol.[1]

Statistical analyses were performed using Stata (version 13.0) and R (version 3.1.1). The observed 10-year risk of CVD events and baseline survival rate were calculated using sex-specific Kaplan-Meier estimates. Participants who died from non-CVD causes were censored at the time of death. The predicted risk of CVD events for each participant was calculated using the FRS. Participants were grouped into deciles of observed and predicted risk within 10 years of follow-up. The FRS was recalibrated by substituting the baseline survival rate and mean risk factor levels with data from the cohort, and the predictive performance of the models was evaluated. Calibration refers to the degree of agreement between observed and predicted events and was measured by the Hosmer-Lemeshow test, with χ^2 <20 indicating good calibration.

Results

A total of 10 291 men and 20 445 women were included in the analysis. Table 1 shows the baseline characteristics of the cohort according to the FRS predictors. The observed 10-year risk of CVD events was 31.0% in men and 18.6% in women. Applying the original FRS function and assuming a ratio of 8:1 for non-fatal to fatal CVD events, the mean predicted 10-year risk of CVD events was 38.5% (95% confidence interval [CI]=38.2%-38.8%) in men and 21.6% (95% CI=21.5%-21.8%) in women. The original FRS function overestimated the 10-year risk of CVD events, especially at the highest risk deciles (Fig). Calibration was poor for both men (χ^2=367.6) and women (χ^2=258.6) [Table 2]. Recalibration using cohort data improved the model's performance slightly in men (χ^2=218.6) but not in women (χ^2=303.0). Applying the recalibrated FRS function, the mean predicted 10-year risk of CVD events was 36.1% (95% CI=35.8%-36.4%) in men and 22.2% (95% CI=22.0%-22.3%) in women.

Discussion

In this large cohort of Hong Kong Chinese older adults, the FRS overestimated the 10-year risk of CVD events by approximately 1.2-fold in both men and women, particularly at the highest risk deciles. This is consistent with the findings of the Chinese Multi-provincial Cohort Study of 30 121 Chinese adults aged 35 to 64 years, which reported that the FRS systematically overestimated CVD risk in men and women, with larger differences in higher risk deciles.[2] The Asia-Pacific Cohort Studies Collaboration also showed that the FRS overestimated risk of CVD by 11% and 10% for men and women, respectively, among six cohorts of 25 682 Chinese adults.[3] Recalibration substantially improved the model's performance in these two studies. In the Hong Kong Cardiovascular Risk Factors Study with a cohort of 2895 Chinese adults aged 25 to 74 years, the FRS overestimated CVD risk by about 1.5-fold in men, although it was relatively accurate when applied to women.[5] In our

TABLE 1. Baseline characteristics of the Elderly Health Service cohort by sex

Characteristics	Men (n=10 291)*	Women (n=20 445)*
Age, y	69.4±2.7	69.3±2.7
Body mass index, kg/m^2	23.9±3.3	24.6±3.7
Systolic blood pressure, mm Hg	146.5±23.1	147.2±23.9
Untreated	144.4±23.3	144.1±23.6
Treated	152.6±21.4	154.9±22.8
Hypertension	2643 (25.7)	5953 (29.1)
Smoking	2227 (21.6)	663 (3.2)
Diabetes	1389 (13.5)	2682 (13.1)

* Data are presented as mean±standard deviation or No. (%) of participants

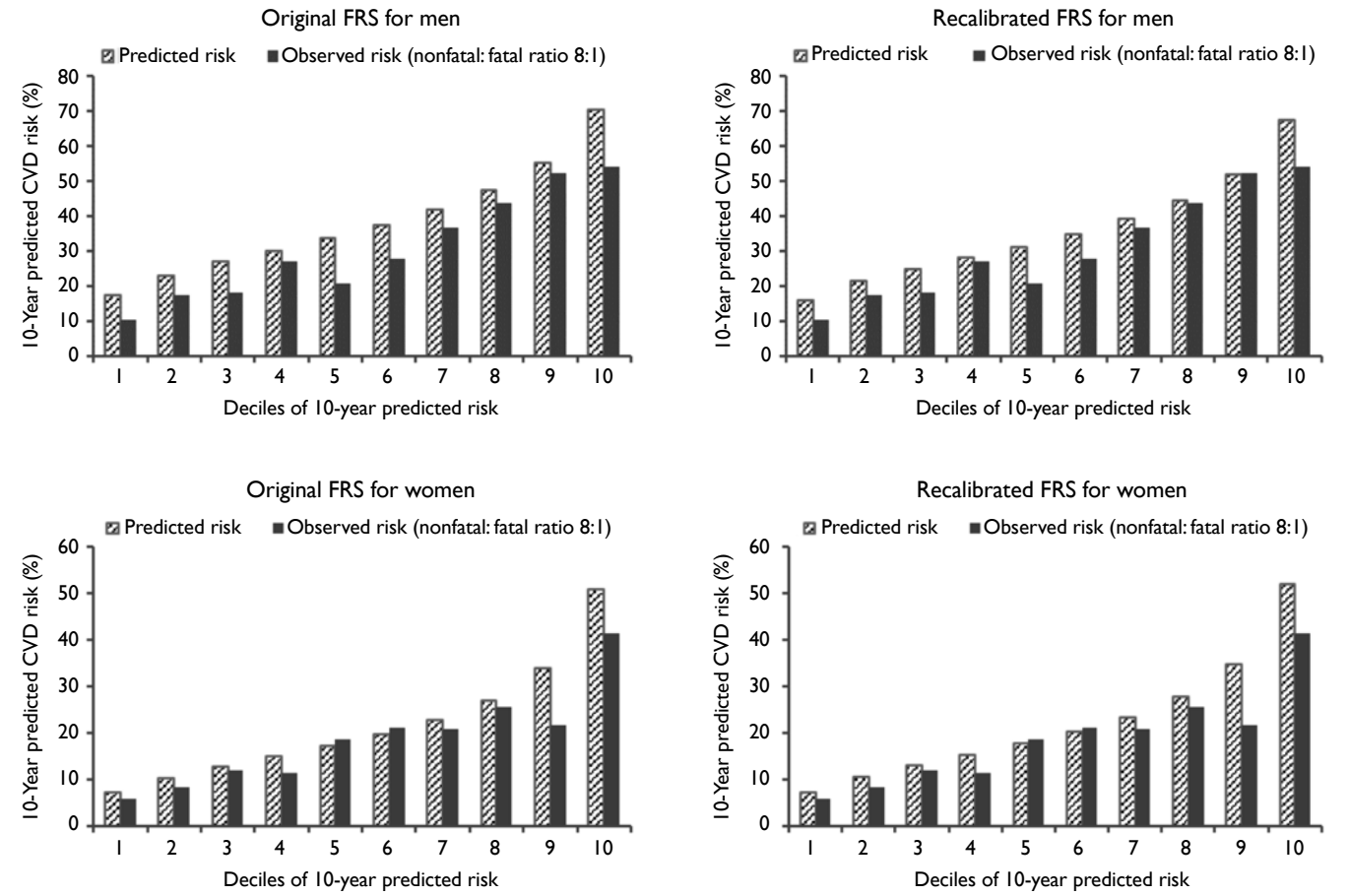


FIG. Prediction of 10-year risk of cardiovascular disease (CVD) events by sex using the original and recalibrated Framingham risk scores (FRS)

TABLE 2. Calibration of the Framingham risk score by sex*

Parameter	Men		Women	
	Original	Recalibrated	Original	Recalibrated
Mean 10-year risk of cardiovascular disease events, % (n)				
Observed†	31.0 (3186)	31.0 (3186)	18.6 (3809)	18.6 (3809)
Predicted	38.5 (3961)	36.1 (3712)	21.6 (4426)	22.2 (4531)
Calibration				
Hosmer-Lemeshow χ^2 statistic	367.6	218.3	258.6	303.0
Hosmer-Lemeshow P value	<0.001	<0.001	<0.001	<0.001

* Discrimination could not be determined, as we did not have data on individual cardiovascular disease events

† Based on a ratio of 8:1 for non-fatal to fatal cardiovascular disease events and Kaplan-Meier estimation for 10 years of follow-up

cohort, recalibration did not improve the model's calibration for women, perhaps because we did not assess laboratory predictors. As we did not measure high-density lipoprotein cholesterol, we were unable to evaluate the FRS based on laboratory predictors, as was in the Chinese Multi-provincial Cohort Study and the Hong Kong Cardiovascular Risk Factors Study cohorts,[2,5] although the office-based FRS has shown good internal validity.[1] Nonetheless, our results should be interpreted with caution owing to the lack of CVD incidence data.

To our knowledge, this was the first study to assess the predictive performance of the FRS for older adults in Hong Kong. Our cohort has the advantages of large sample size and long duration of follow-up. Nonetheless, there were several limitations. First, participants in the cohort were volunteers and may have been healthier and/or more health-conscious

than the general population, although the two groups were largely comparable in terms of socioeconomic status and health services use.[4] The FRS was derived from a cohort of volunteers. Older adults in long-term care facilities or with very poor health were unlikely to attend the elderly health centres. Survivor bias may be a problem if those who are particularly prone to certain types of exposure died before they could be recruited.[4] This is a problem inherent to all cohorts of older adults. Second, high-density lipoprotein cholesterol was not measured; hence, the laboratory-based version of the FRS could not be validated. Nonetheless, the office-based FRS has similar predictive performance to that of the laboratory-based version.[1] Third, only estimates of CVD events were provided because participants were not actively followed up, although the FRS still overestimated the risk according to a conservative assumption of the case-fatality ratio. We were unable to assess discrimination by the FRS, as we did not have individual data on CVD events. Nonetheless, even if participants had been followed up actively, the adjudication of CVD events in such a large sample would have been extremely labour-intensive and costly. Fourth, CVD risk prediction tools are used to guide clinical decisions on risk factor modification, such as lipid-lowering therapy. However, we were unable to assess whether participants were already on such therapy at baseline, which could result in overestimation of CVD risk. Finally, we relied on routine mortality data for classification of CVD deaths, which is more prone to misclassification than autopsy data. Nonetheless, most deaths in Hong Kong occur in hospitals; this enables relatively accurate ascertainment of the causes of death.

Conclusions

The FRS systematically overestimated CVD risk in older Hong Kong Chinese adults despite recalibration. The FRS should be used with caution. Overestimation of risk may result in unnecessary healthcare costs and potential harms associated with statin therapy. The risk factors for CVD may vary across populations. New risk prediction models that account for CVD incidence data should be developed.

Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#12133051). We thank the Department of Health for their collaboration with the Elderly Health Service Cohort.

References

1. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743-53.
2. Liu J, Hong Y, D'Agostino RB Sr, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. JAMA 2004;291:2591-9.
3. Asia Pacific Cohort Studies Collaboration, Barzi F, Patel A, et al. Cardiovascular risk prediction tools for populations in Asia. J Epidemiol Community Health 2007;61:115-21.
4. Schooling CM, Chan WM, Leung SL, et al. Cohort profile: Hong Kong Department of Health Elderly Health Service Cohort. Int J Epidemiol 2016;45:64-72.
5. Lee CH, Woo YC, Lam JK, et al. Validation of the pooled cohort equations in a long-term cohort study of Hong Kong Chinese. J Clin Lipidol 2015;9:640-6.e2.

Lifestyle intervention in obese Chinese adolescents with non-alcoholic fatty liver disease: a randomised controlled study

DFY Chan*, EAS Nelson, AM Li, J Woo, MM Sea, RSM Chan, WCW Chu, M Chan, HK So

KEY MESSAGE

A 16-week lifestyle intervention effectively reduced body fat and intra-hepatic triglyceride content in obese Chinese adolescents with non-alcoholic fatty liver disease.

Hong Kong Med J 2018;24(Suppl 4):S12-5
HMRF project number: 11122981

[1] DFY Chan, [1] EAS Nelson, [1] AM Li, [2] J Woo, [2] MM Sea, [2] RSM Chan, [3] WCW Chu, [4] M Chan, [1] HK So

The Chinese University of Hong Kong:
[1] *Department of Paediatrics*
[2] *Department of Medicine and Therapeutics & Centre for Nutritional Studies*
[3] *Department of Imaging and Interventional Radiology*
[4] *Department of Chemical Pathology*

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

Introduction

The incidence of non-alcoholic fatty liver disease (NAFLD) has increased because of the growing prevalence of obesity and overweight in the paediatric population.[1] NAFLD is one of the most common forms of chronic liver disease in children.[1] Lifestyle intervention is the main management approach. Although a lifestyle modification programme involving diet restriction and physical exercise provides beneficial effects for adults with NAFLD, there is limited evidence of its efficacy in adolescents. The present study evaluated the efficacy of a lifestyle modification programme at reversing and reducing NAFLD in obese adolescents.

Participants and Methods

The study was approved by the Joint Chinese University of Hong Kong and New Territories East Cluster Clinical Research Ethics Committee. Written informed consent was obtained from the parents and/or participants. The study was conducted in compliance with the Declaration of Helsinki and International Conference on Harmonisation-Good Clinical Practice.

Post-pubertal obese Chinese adolescents aged 14 to 18 years with body mass index (BMI) ≥95th percentile of the local reference[2] and who attended the Obesity and Lipid Disorder Clinic at Prince of Wales Hospital, Hong Kong were invited to participate. Their intra-hepatic triglyceride content (IHTC) was measured at baseline and week 16 using proton magnetic resonance spectroscopy (^{1}H-MRS) with a whole-body 3-Tesla scanner (Achieva TX; Philips Healthcare, Best, the Netherlands) by a trained investigator blinded to group allocation. Fatty liver was defined as the presence of hepatic steatosis ≥5% fat content level.

Participants were randomised to the intervention (lifestyle modification programme) or control group. In the intervention group, counselling sessions were provided weekly for the first 4 months and then bi-monthly for 52 weeks. The lifestyle modification programme aims to improve knowledge, attitude, and practice regarding diet and exercise based on motivational interviewing and behavioural modification. In the control group, diet and exercise advice was provided during routine consultations at the Obesity Clinic every 4 months by attending physicians.

Anthropometrics including body height, weight, BMI, and percentage of body fat were measured at baseline, week 16, and week 68, as well as dietary records and laboratory tests.

Between-group and within-group comparisons were made at baseline, week 16, and week 68 using paired or independent *t* tests, the Chi squared test, or Fisher's exact test, as appropriate. Logistic regression was used to determine NAFLD remission at week 16 based on the ^{1}H-MRS, anthropometric, and laboratory results. Per-protocol analysis was performed among adherent participants. All statistical tests were two-sided, and a P value of <0.05 was considered statistically significant. SPSS (for Windows, version 21; IBM Corp, Armonk, NY, US) was used for all statistical analyses.

Results

A total of 79 obese adolescents aged 14 to 18 years were invited for NAFLD screening and assessed by ^{1}H-MRS between February and March 2014. Of these,

52 were diagnosed with NAFLD and randomised to the intervention (n=26) or control (n=26) group (Fig). At baseline, the two groups were well-matched in terms of demographic characteristics, clinical and laboratory data, and IHTC measurements (Table 1).

At week 16, four participants in the intervention group had withdrawn owing to poor motivation (n=2), tight schedule (n=1), or study abroad (n=1); and two participants in the control group had withdrawn owing to tight schedule (n=2). Therefore, 22 participants in the intervention group and 24 participants in the control group were included in the per-protocol analysis. The compliance rate was 85% in the intervention group and 92% in the control group. None of the participants were using weight loss agents or lipid-lowering drugs.

The between-group difference in the change of IHTC from baseline to week 16 was significant (P=0.029), and the mean reduction in the proportion of IHTC from before to after intervention was significantly greater in the intervention group than the control group (30.5% vs 7.5%, P<0.001, Table 2). Ten (19%) of the 52 participants (six in the intervention group and four in the control group) had complete remission of NAFLD at 16 weeks. The aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ratio, insulin, and homeostasis model assessment (HOMA) also improved significantly, paralleling the reduction in body size in the intervention group (Table 2). Multivariate analysis showed only reduction in body fat and baseline IHTC as independent factors associated with NAFLD remission (Table 3).

At week 68, two participants in each group were lost to follow-up during the maintenance phase. Therefore, 20 participants in the intervention group and 22 participants in the control group were included in the per-protocol analysis. Participants who completed or did not complete assessment at week 16 or week 68 were similar in terms of baseline body size and IHTC.

After the intervention, the mean BMI z-score of the intervention group was reduced to 2.2, whereas that of the control group was non-significantly

TABLE 1. Baseline characteristics of participants with non-alcoholic fatty liver disease

Variable	Intervention (n=26)*	Control (n=26)*
Age, y	15.3±3.4	13.8±5.3
Male sex	16 (61.5)	17 (65.4)
Body weight, kg	91.1±9.8	91.1±8.0
Male	93.7±7.7	91.4±8.2
Female	87.0±11.6	90.3±7.8
Body mass index, kg/m^2	32.59±3.28	32.12±3.12
Male	32.26±3.11	31.23±2.92
Female	33.14±3.63	34.12±2.75
Body mass index z-score	2.32±0.38	2.29±0.37
Male	2.18±0.28	2.12±0.29
Female	2.54±0.42	2.68±0.22
Waist circumference, cm	103.9±9.7	103.6±7.8
Male	106.0±9.8	103.1±8.2
Female	100.5±8.8	104.7±7.1
Body fat, %	41.1±8.5	39.0±9.1
Male	38.4±7.4	34.2±5.5
Female	45.5±8.7	49.8±5.3
Alanine aminotransferase, IU/L	38.9±25.6	36.7±26.6
Aspartate aminotransferase, IU/L	22.5±7.8	23.4±9.5
Aspartate aminotransferase / alanine aminotransferase ratio	0.68±0.23	0.80±0.37
Insulin, mIU/L	27.4±16.2	27.8±23.2
Fasting glucose, mmol/L	5.0±0.4	4.9±0.5
Homeostasis model assessment	6.3±4.2	5.3±3.1
Quantitative insulin-sensitivity check index	0.50±0.07	0.52±0.12
Intra-hepatic triglyceride content, %	13.1±7.8	13.5±10.2

* Data are presented as mean±standard deviation or No. (%) of participants

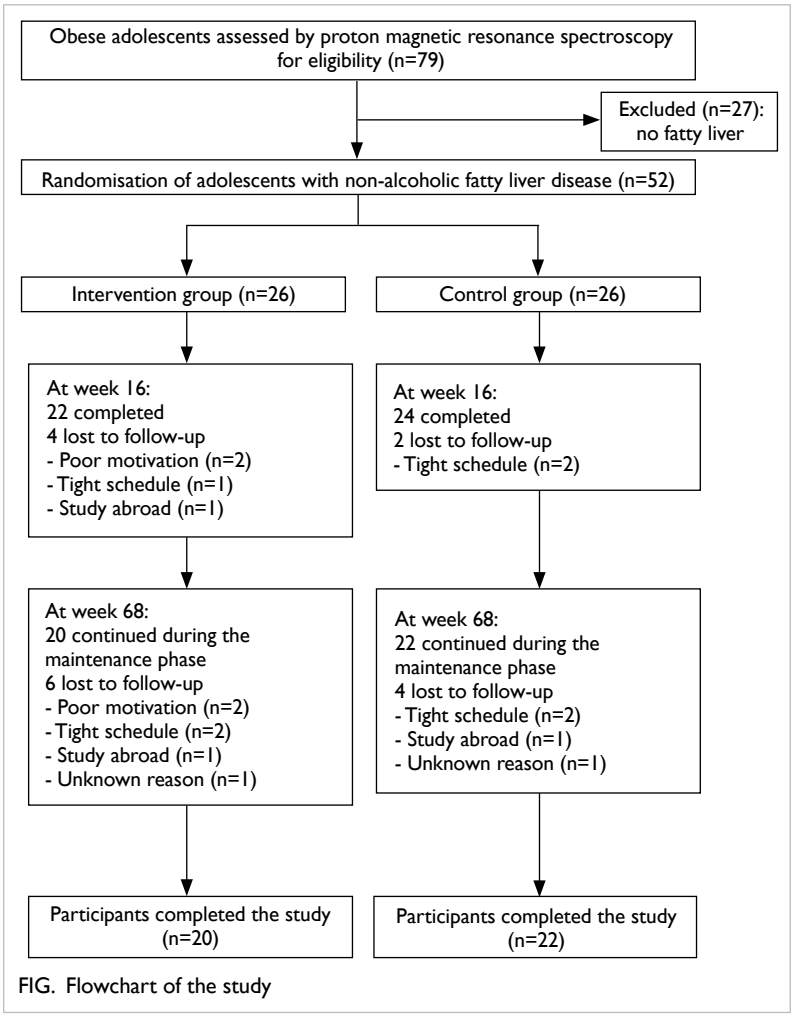


FIG. Flowchart of the study

TABLE 2. Clinical and laboratory characteristics of participants at 16 weeks and 68 weeks

	Baseline	Baseline to 16 weeks			Baseline to 68 weeks		
		Within-group difference	Between-group difference in change		Within-group difference	Between-group difference in change	
	Mean±SD	Mean±SD	Mean±SE	P value	Mean±SD	Mean±SE	P Value
Body weight, kg							
Control	91.1±8.0	–0.7±2.9	Reference		–0.08±7.16	Reference	
Intervention	91.1±9.8	–5.2±5.4*	–4.5±1.3	0.001	–1.60±6.49	–1.52±2.19	0.472
Body mass index, kg/m^2							
Control	32.1±3.1	–0.37±0.95	Reference		–0.69±2.15	Reference	
Intervention	32.6±3.3	–1.8±1.6*	–1.45±0.38	0.001	–0.79±2.01	–0.10±0.65	0.882
Body mass index z-score							
Control	2.3±0.4	–0.03±0.08	Reference		–0.07±0.21	Reference	
Intervention	2.3±0.4	–0.19±0.17*	–0.16±0.04	<0.001	–0.05±0.18	0.02±0.64	0.808
Waist circumference, cm							
Control	103.6±7.8	3.1±5.2*	Reference		–0.16±6.95	Reference	
Intervention	103.9±9.7	–0.6±5.0	3.71±1.51	0.018	–1.04±6.26	0.88±2.02	0.831
Body fat, %							
Control	39.0±9.1	1.0±4.2	Reference		0.86±6.27	Reference	
Intervention	41.1±8.5	–3.1±4.0*	–4.12±1.21	0.001	–3.81±6.02*	–4.67±1.88	0.017
Alanine aminotransferase, IU/L							
Control	36.7±26.6	–4.4±8.7	Reference		10.00±53.98	Reference	
Intervention	38.9±25.6	–4.10±16.5	0.30±3.86	0.610	5.41±22.63	–4.59±12.48	0.715
Aspartate aminotransferase, IU/L							
Control	23.4±9.5	–0.9±5.4	Reference		6.91±23.60	Reference	
Intervention	22.5±7.8	–0.70±5.64	0.18±1.67	0.917	7.40±11.27	0.49±5.78	0.933
Aspartate aminotransferase / alanine aminotransferase ratio							
Control	0.80±0.37	0.02±0.14	Reference		0.09±0.27	Reference	
Intervention	0.68±0.23	0.12±0.17*	0.11±0.05	0.052	0.13±0.26*	0.04±0.08	0.650
Insulin, mIU/L							
Control	27.8±23.2	–0.88±18.29	Reference		–2.43±21.88	Reference	
Intervention	27.4±16.2	–4.98±10.86*	–4.10±4.49	0.366	–0.62±10.38	3.06±5.31	0.507
Fasting glucose, mmol/L							
Control	4.9±0.5	0.12±0.29	Reference		0.07±0.31	Reference	
Intervention	5.0±0.4	–0.11±0.39	–0.23±0.12	0.039	0.03±0.47	–0.04±0.12	0.771
Homeostasis model assessment							
Control	5.3±3.1	0.8±2.70	Reference		0.32±1.92	Reference	
Intervention	6.3±4.2	–1.2±1.90*	–2.00±0.80	0.018	0.23±2.69	–0.11±0.81	0.894
Quantitative insulin-sensitivity check index							
Control	0.52±0.12	–0.04±0.11	Reference		2.23±0.32*	Reference	
Intervention	0.50±0.07	0.03±0.06	–0.01±0.03	0.043	2.28±0.31*	0.05±0.10	0.509
Intra-hepatic triglyceride content, %							
Control	13.5±10.2	–0.96±4.18	Reference		-	-	-
Intervention	13.1±7.8	–4.02±5.02*	–3.1±1.36	0.029	-	-	-
Abdominal adipose tissue, mL							
Control	16456.8±2715.5	593.7±1697.2	Reference		-	-	-
Intervention	16002.3±3709.5	–795.8±1918.1	-1389.5±533.10	0.012	-	-	-
Subcutaneous abdominal adipose tissue, mL							
Control	13640.2±2341.4	243.5±1091.7	Reference		-	-	-
Intervention	13038.7±3432.2	–727.1±1575.1*	–970.6±403.04	0.019	-	-	-
Visceral adipose tissue, mL							
Control	2816.6±786.8	350.2±1108.5	Reference		-	-	-
Intervention	2963.6±865.9	–68.8±834.9	–419.0±291.45	0.158	-	-	-

Abbreviations: SD=standard deviation; SE = standard error

* P<0.05, paired t-test within group

reduced by 0.07. Body fat was significantly lower in the intervention group than the control group (mean difference=4.6%, P=0.025, Table 2). The IHTC, quantitative insulin sensitivity check index, and high-density lipoprotein cholesterol level were improved significantly in both groups compared with baseline (Table 2). The improvement in the AST/ALT ratio from baseline to week 68 was significant in the intervention group (P=0.017). The proportion of participants with insulin resistance (HOMA >3) did not differ significantly between groups (16/20 vs 15/22, P=0.384).

TABLE 3. Factors associated with remission of non-alcoholic fatty liver disease at week 16

Factor	Univariate		Multivariate	
	Odds ratio (95% confidence interval)	P value	Adjusted odds ratio (95% confidence interval)	P value
Intervention group	1.875 (0.451-7.802)	0.388	0.392 (0.034-4.519)	0.453
Age	0.730 (0.362-1.473)	0.379		
Baseline intra-hepatic triglyceride content	0.596 (0.375-0.950)	0.029	0.431 (0.209-0.889)	0.023
Baseline body weight	0.988 (0.912-1.071)	0.771		
Change in body weight	0.704 (0.549-0.902)	0.006		
Baseline body mass index	0.852 (0.663-1.095)	0.211		
Change in body mass index	0.387 (0.200-0.749)	0.005		
Baseline body mass index z-score	0.238 (0.031-1.809)	0.165		
Change in body mass index z-score	0.000 (0.000-0.029)	0.002		
Baseline body fat	0.890 (0.801-0.990)	0.031		
Change in body fat	0.826 (0.686-0.994)	0.044	0.687 (0.483-0.975)	0.036
Baseline abdominal adipose tissue	1.000 (1.000-1.000)	0.148		
Change in abdominal adipose tissue	1.000 (0.999-1.000)	0.137		
Baseline subcutaneous abdominal adipose tissue	1.000 (1.000-1.000)	0.242		
Change in subcutaneous abdominal adipose tissue	0.999 (0.999-1.000)	0.042		
Baseline visceral adipose tissue	0.999 (0.998-1.000)	0.122		
Change in visceral adipose tissue	1.000 (0.999-1.001)	0.760		

Discussion

The 16-week lifestyle modification programme significantly reduced IHTC, body size, and subcutaneous abdominal adipose tissue. The laboratory variables, including AST/ALT ratio, insulin, and HOMA, improved significantly in the intervention group. Body fat and baseline IHTC were independent factors associated with NAFLD remission at week 16. This indicates that the effects of the programme were largely mediated by body fat reduction and baseline IHTC. Body fat reduction improved not only liver condition (AST/ALT ratio and IHTC) but also insulin resistance indices (HOMA and quantitative insulin sensitivity check index). Insulin resistance is a common finding in paediatric patients with NAFLD.[3] Weight loss in healthy adults can improve insulin sensitivity and lower the risk of diabetes conferred by insulin resistance.[4] This may partially explain the programme's beneficial effects of improving the AST/ALT ratio, insulin levels, and HOMA. Baseline IHTC was associated with remission of NAFLD in both groups.

There are limitations to our study. The nature of the study did not allow blinding of study participants. Liver biopsy was not performed to evaluate the presence of necrosis and inflammation. Nonetheless, ^{1}H-MRS enables an accurate assessment of IHTC,[5] and the technicians were blinded to the grouping. Further studies are required to determine the long-term prognoses of development of fibrosis, mortality, and quality of life and their modification by weight reduction.

Conclusion

Childhood obesity has significant medical and socio-economic impacts on society. NAFLD is an important obesity-related complication. The 16-week lifestyle modification programme effectively reduced body fat and IHTC in obese Chinese adolescents with NAFLD.

Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#11122981), and the University Grants Council. The authors also thank all the participants and their parents.

References

1. Widhalm K, Ghods E. Nonalcoholic fatty liver disease: a challenge for pediatricians. Int J Obes (Lond) 2010;34:1451-67.
2. Leung SS, Cole TJ, Tse LY, Lau JT. Body mass index reference curves for Chinese children. Ann Hum Biol 1998;25:169-74.
3. Manco M, Marcellini M, Devito R, Comparcola D, Sartorelli MR, Nobili V. Metabolic syndrome and liver histology in paediatric non-alcoholic steatohepatitis. Int J Obes (Lond) 2008;32:381-7.
4. Conn VS, Koopman RJ, Ruppar TM, Phillips LJ, Mehr DR, Hafdahl AR. Insulin sensitivity following exercise interventions: systematic review and meta-analysis of outcomes among healthy adults. J Prim Care Community Health 2014;5:211-22.
5. Wong VW, Chu WC, Wong GL, et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. Gut 2012;61:409-15.

Psychometric properties of the Chinese Post-traumatic Growth Inventory in patients with chronic diseases

CHK Cheng *, SMY Ho, TL Rochelle

KEY MESSAGE

The Chinese version of the Post-traumatic Growth Inventory is a reliable and valid instrument to assess the post-traumatic growth of Hong Kong Chinese patients with chronic disease.

Hong Kong Med J 2018;24(Suppl 4):S16-9
HMRF project number: 11122671

CHK Cheng, SMY Ho, TL Rochelle

Department of Social and Behavioural Sciences, City University of Hong Kong

* Principal applicant and corresponding author: sshkc@cityu.edu.hk

Introduction

After exposure to traumatic events, negative outcomes such as anxiety and stress disorders are often reported. However, positive changes, or post-traumatic growth (PTG), have also been increasingly documented[1] and can be reflected in self-perception, a changed sense of relationship with others, and a changed philosophy of life.[2] The Post-traumatic Growth Inventory (PTGI) has been widely used to measure PTG in five domains: appreciation of life, new possibilities, personal strength, spiritual change, and relating to others.[3]

Although the reliability of the PTGI has generally been supported, its psychometric properties among Chinese people remain unconfirmed. In a study of mainland Chinese people with skin disease, PTG has been understood as self-growth, new possibilities, and appreciation of life. Nonetheless, in studies of Chinese patients with cancer in Hong Kong and Taiwan, a higher-order model of PTG has been supported.[4,5] The PTGI has not been validated in patients with non-cancer chronic conditions in Hong Kong. This study aimed to examine the psychometric properties of the Chinese version of the PTGI (CPTGI) among patients with chronic disease in terms of internal consistency, reliability, concurrent validity, underlying measurement model, and test-retest reliability.

Methods

Using stratified sampling, nine non-governmental organisations and parents' self-help groups from different districts were randomly selected. The targeted participants were first screened by the officers. The inclusion criteria were: (1) Chinese adult patients in Hong Kong with any kind of chronic illness; (2) currently under medical treatment for the illness; (3) non-cancerous or no cancer history; and (4) no cognitive or psychiatric impairments.

The participants were told that the purpose of the study was to understand their psychological well-being after having been diagnosed with chronic illnesses. Informed consent was obtained from each participant before data collection. A subsample of the respondents (n=122) were randomly selected for a follow-up survey after 1 to 9 weeks to assess the test-retest reliability of the CPTGI.

The questionnaire consisted of demographic variables (age, sex, chronic disease, time of diagnosis, marital status, accommodation) and psychometric scales that assess PTG, anxiety and depression, hope, and coping. The CPTGI measures positive changes experienced by patients after a major life crisis. It comprises 21 items in the domains of appreciation of life, new possibilities, relating to others, personal strength, and spiritual change. The Chinese version of the Hospital Anxiety and Depression Scale comprises 14 items: half on depression and half on anxiety. The Chinese version of the Adult Trait Hope Scale measures an individual's hope on two subscales: pathways (4 items) for individual appraisals of the capability to surmount barriers and strive for goals, and agency (4 items) to assess individual general determination with respect to goals. The short version of the Coping Orientation to Problems Experienced scale comprises 28 items on 14 coping strategies: active coping, planning, positive reframing, acceptance, humour, religion, using emotional support, using instrumental support, self-distraction, denial, venting, substance use, behavioural disengagement, and self-blame.

Results

A total of 265 patients were included. Their mean age was 72.95 (standard deviation, 14.85; range, 20-100) years. Most (61%) had a primary education or lower.

Most (54%) were married. About 28% lived with their parents and/or children, 26% lived with spouses, 22% were solitary, and 19% lived in caring or nursing homes. Most (61%) took care of themselves, but 24% received care from family members, 12% from caring or nursing homes, and 3% from domestic helpers. The mean time since primary disease diagnosis was 3.88 (standard deviation, 3.28; range, 0-10) years. Diagnoses included hypertension (n=50), coronary heart disease (n=37), diabetes (n=26), Parkinson disease (n=26), stroke (n=19), and other chronic illnesses (rheumatoid arthritis, low back pain, and cardiac dysrhythmia).

All scales had satisfactory internal consistency reliability, with Cronbach's alpha ranging 0.66 to 0.85 (Table 1). No gender differences were significant on any scale or subscale.

Confirmatory factor analysis was conducted on the covariance matrix of the CPTGI scores. Competing models were specified according to the literature and included the original five-factor first-order model, a three-factor first-order model, a higher-order model, and a higher-order model without item 15 (Table 2).[3-5]

The two first-order models had poorer fit than the higher-order models, in which self, life orientation, and spiritual were combined under a latent factor (intrapersonal), whereas interpersonal was the fourth factor on its own. Removal of item 15 (as suggested in a study)5 did not generate a significantly better fit. The higher-order model in which all items were retained was adopted (Fig). Our hypothesis was supported by the results: PTG can be understood as a four-factor construct (self, spiritual, life orientation, interpersonal) in which a higher-order factor (intrapersonal) includes the self, spiritual, and life orientation factors.

The concurrent validity of the CPTGI was examined by Pearson's correlations among all scales. Overall, the CPTGI correlated positively with hope (r=0.37) and coping (r=0.32) but negatively with anxiety and depression (r= −0.21), as predicted. These inter-factor relationships supported the construct validity of the CPTGI. Nonetheless, owing to fatigue, only a few participants could finish all four scales. Thus, interpretations of correlations between the Adult Trait Hope Scale and Coping Orientation to Problems Experienced scale should be cautious.

TABLE 1. Internal consistency and reliability of scales

Scale	No. of items	Male	Female	Total	Cronbach's alpha
Chinese version of Post-traumatic Growth Inventory	21	2.69±0.84	2.63±0.97	2.64 ±0.92	0.93
Appreciation of life	3	8.77±2.99	8.22±3.84	8.42±3.51	0.66
New possibilities	5	11.69±5.77	11.52±6.22	11.58±6.01	0.85
Relating to others	7	20.21±6.56	19.90±7.37	19.92±7.08	0.85
Personal strength	4	12.31±3.46	12.58±4.33	12.40±4.05	0.76
Spiritual change	2	4.88±2.92	4.82±3.03	4.82±2.97	0.66
Chinese version of Hospital Anxiety and Depression Scale	14	1.75±0.38	1.82±0.33	1.78±0.35	0.82
Anxiety	7	2.23±0.74	2.34±0.61	2.29±0.68	0.69
Depression	7	1.25±0.31	1.29±0.32	1.27±0.31	0.77
Chinese version of Adult Trait Hope Scale	8	6.07±1.43	5.02±1.42	5.65±1.47	0.86
Pathway	4	6.06±1.47	5.08±1.86	5.67±1.65	0.77
Agency	4	6.08±1.51	4.96±1.34	5.63±1.51	0.73
Coping Orientation to Problems Experienced scale	28	2.47±0.39	2.60±0.41	2.52±0.39	0.80

TABLE 2. Goodness-of-fit indices of different factor models

Factor model	χ^2	Degrees of freedom	χ^2 / degrees of freedom	Goodness-of-fit index	Adjusted goodness-of-fit index	Comparative fit index	Tucker-Lewis index	Root mean square error of approximation	Standardised root mean square residual
Original five-factor first-order model	394.203	179	2.20	0.874	0.837	0.917	0.903	0.0670	0.0480
Three-factor first-order model	343.374	132	2.60	0.867	0.827	0.900	0.884	0.078	0.0531
Higher-order model	170.153	87	1.95	0.924	0.895	0.946	0.934	0.060	0.0445
Higher-order model without item 15	147.354	74	1.99	0.929	0.899	0.949	0.937	0.061	0.0437

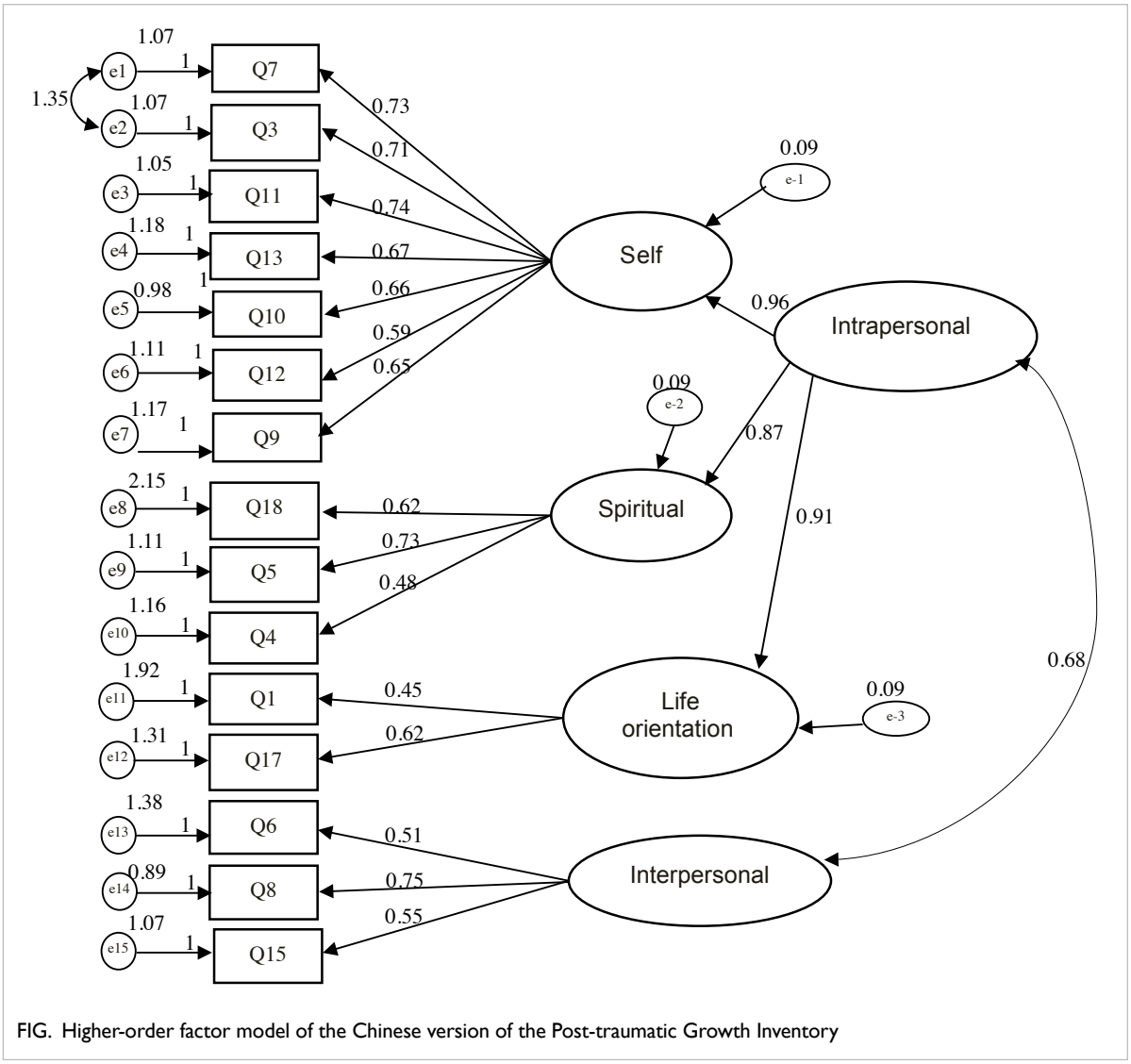


FIG. Higher-order factor model of the Chinese version of the Post-traumatic Growth Inventory

In summary, the more hope a patient saw in life after experiencing trauma, the more growth he/she perceived. With regard to coping, positive coping strategies (positive reframing, religion, planning) correlated positively with PTG, but negative coping correlated negatively with PTG. The results of the PTGI correlated negatively with anxiety (r= −0.15 to −0.23).

The test-retest reliability values of CPTGI scores at weeks 1 and 9 were analysed using Pearson's product-moment correlation and dependent *t*-tests. All paired *t*-tests of within-subject differences were non-significant, indicating that there was no significant change between pre-test and post-test scores. Pearson's correlations between the test/retest scores on all subscales and the total scale were significant, but not high (r=0.33 to 0.44).

Discussion

The CPTGI is a reliable and valid instrument for assessment of PTG in Chinese patients with chronic disease. All items should be included in the measurement of total PTG and domain-specific PTG; deletion of any item is not advisable. On the subscale level, the original five subscales had better internal consistency reliability than the four first-order factors had. This suggests that when measurement of specific domains of PTG is of concern, the original subscales should be adopted. When the overall PTG of patients is of interest, the higher-order model can be referenced, for instance, when designing a PTG enhancement programme for patients.

The concurrent validity of the CPTGI was also satisfactory. Overall, PTG was associated positively with hope and positive coping but negatively with

anxiety. Under the higher-order model, anxiety was related to intrapersonal growth but not interpersonal growth. The higher anxiety an individual had, the lower was his/her level of intrapersonal growth. Depression did not have a significant association with PTG (but this could be caused by the small sample size).

Based on the correlation between PTG and hope, we may interpret that when one acquires new understanding and perceptions of the self, one may acquire a higher capacity to surmount obstacles and grow even after trauma. Moreover, one may have stronger determination to overcome difficulties when he/she can appreciate new spiritual experiences after trauma.

Positive coping strategies (such as positive reframing, religion, and planning) were beneficial to PTG, whereas negative coping strategies (such as denial and substance use) may impede PTG. The associations between negative coping and PTG domains were as strong as that between positive coping and PTG. Health practitioners should focus not only on strengthening positive coping but also on reducing negative coping.

Health practitioners may use the CPTGI to assess the PTG of patients with chronic diseases to improve monitoring of patients' emotional and cognitive conditions. For example, specific vulnerable domains in individuals' post-traumatic well-being can be easily identified and managed with intervention programmes.

Our study has provided empirical support for the test-retest reliability of the CPTGI. This is crucial for an instrument that measures PTG, which is a long-term process for some people.

Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#11122671). We would like to thank the participating centres for their coordination and facilitation and the participants for their cooperation and patience despite their chronic illnesses.

References

1. Helgeson VS, Reynolds KA, Tomich PL. A meta-analytic review of benefit finding and growth. J Consult Clin Psychol 2006;74:797-816.
2. Tedeschi RG, Calhoun LG. Posttraumatic growth: conceptual foundations and empirical evidence. Psychol Inq 2004;15:1-18.
3. Tedeschi RG, Calhoun LG. The Posttraumatic Growth Inventory: measuring the positive legacy of trauma. J Trauma Stress 1996;9:455-71.
4. Zhai J, Huang Y, Gao X, Jiang H, Xu J. Post-trauma growth in a Mainland Chinese population with chronic skin disease. Int J Dermatol 2014;53:450-7.
5. Ho SM, Law LS, Wang GL, Shih SM, Hsu SH, Hou YC. Psychometric analysis of the Chinese version of the Posttraumatic Growth Inventory with cancer patients in Hong Kong and Taiwan. Psychooncology 2013;22:715-9.

Formula-feeding and the risk of type-2 diabetes mellitus among Hong Kong adolescents

LL Hui, SL Lee, MK Kwok, CW Yu, CM Schooling*

KEY MESSAGES

1. Compared with exclusive breastfeeding, formula-feeding in the first 3 months of life is associated with poorer lipid profile and possibly greater insulin resistance but not greater adiposity at age 17.5 years.
2. Early infant nutrition may affect long-term health; therefore, breastfeeding should be encouraged.
3. Further studies are warranted, to investigate the effects of infant feeding on glucose metabolism and insulin resistance later in life.

Hong Kong Med J 2018;24(Suppl 4):S20-3
HHSRF project number: 10111491

[1] **LL Hui**, [2] **SL Lee**, [1] **MK Kwok**, [3] **CW Yu**, [1,4] **CM Schooling**

[1] *School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong*
[2] *Department of Paediatrics and Adolescent Medicine, The University of Hong Kong*
[3] *Department of Health and Physical Education, The Education University of Hong Kong*
[4] *CUNY School of Public Health and Hunter College, New York, USA*

Principal applicant: LL Hui
* Corresponding author: cms1@hku.hk

Introduction

The long-term effects of infant feeding mode on glucose metabolism and risk of type-2 diabetes mellitus (T2DM) remain unclear. In the 1980s, a randomised controlled trial demonstrated that formula-fed preterm infants, compared with breastfed preterm infants, had faster infant growth and greater insulin resistance during adolescence.[1] However, another randomised controlled trial found no effect of breastfeeding on cardiometabolic risk at age 11.5 years.[2] A systematic review of observational studies concluded that breastfeeding was associated with a lower risk of T2DM, compared with formula-feeding.[3] Nonetheless, publication bias and residual confounding by socio-economic status could not be ruled out. This study aimed to assess the association of infant feeding modes with risk factors for T2DM at age 17.5 years in the 'Children of 1997' birth cohort.[4]

Methods

This study was approved by the University of Hong Kong-Hospital Authority Hong Kong West Cluster Joint Institutional Review Board (UW 12-249) and the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CRE-2013.507).

The 'Children of 1997' birth cohort (n=8327) covers 88% of all births from 1 April to 31 May 1997. Families were recruited at their first postnatal visit to the Maternal and Child Health Centres. Baseline characteristics including birth characteristics, parental education, and feeding mode were obtained using a self-administered questionnaire. Information on feeding mode was collected at age 3, 9, and 18 months. Since 2005, passive and active follow-ups have been carried out by means of data linkage and surveys to obtain health-related information.

Several sites were set up for clinical examination of the cohort at age 17.5 years. Fasting blood (30 mL) was drawn from participants in the morning to measure haemoglobin A1c, fasting glucose, insulin, cholesterol, triglyceride, and high-sensitivity C-reactive protein (hs-CRP). Body weight, % body fat, % muscle, standing height, waist circumference, and hip circumference were measured based on standard protocols. Handgrip strength (a proxy for muscle mass) of both hands was measured using a handgrip dynamometer. Pubertal stages were self-reported using line drawings of models at each Tanner stage.

Infant feeding mode at age 0-3 months was categorised as always formula-fed, mixed feeding, or exclusively breastfed. The duration of formula-feeding was categorised as 0-2 years, 3-5 years, or 6 years.

General adiposity was proxied by body mass index z-score relative to the 2007 World Health Organization growth reference and % body fat, whereas central adiposity was proxied by waist-to-height ratio z-score. Lean mass was proxied by total muscle mass and handgrip strength. Markers of glucose metabolism included fasting haemoglobin A1c, fasting glucose, fasting insulin, insulin resistance, and insulin sensitivity (estimated by the homeostasis model assessment). Other health markers included lipid profile (ie, total cholesterol), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, triglycerides, and systematic inflammation, proxied by hs-CRP. Log-transformed insulin and hs-CRP levels were used in the analyses.

Multivariable linear regression was used to assess the association of infant feeding mode with diabetes risk factors and other health markers at age 17.5 years. Model 1 adjusted for sex, pubertal stage, and age at follow-up and potential confounders,

including birth weight, gestational age, pregnancy characteristics (gestational diabetes, preeclampsia, and maternal smoking), mother's place of birth, and highest parental education. To test whether infant growth mediated any association, model 2 additionally adjusted for weight gain from birth to 3 months or birth to 12 months, defined in terms of the change in weight z-score. Whether the associations varied by sex and infant growth rate from the significance of interaction terms was tested. To minimise the bias from missing data, multiple imputation and inverse probability weighting were combined and the results summarised from 10 imputed datasets into single estimates.

Results

This study aimed to include 700 participants and finally included 710. Compared with the entire birth cohort, the 315 male and 395 female participants had parents with slightly higher education, a higher rate of gestational diabetes, and less maternal smoking during pregnancy. Clinical examinations were carried out at a mean age of 17.5 years. As expected, males on average were taller with lower % body fat, greater total muscle mass, and greater handgrip strength. Approximately 15% of male and 9% of female participants were overweight according to the International Obesity Task Force cut-offs. Few participants had LDL cholesterol (<1%) or triglycerides (<4%) above normal ranges (4.1 mmol/L and 1.7 mmol/L, respectively). Only five participants had elevated fasting glucose (range, 5.8-7.6 mmol/L), of whom four had normal haemoglobin A1c and one had clinically diagnosed T2DM. In both sexes, greater body mass index was associated with higher fasting glucose, insulin, insulin resistance, LDL cholesterol, triglycerides, and hs-CRP.

Approximately 7% of the participants were exclusively breastfed at 0-3 months; they were more likely to be female, with mainland-born mothers with a lower education level (Table 1). Compared with participants who were exclusively breastfed at 0-3 months, participants who were always formula-fed had less weight gain at 0-3 months, but not at 0-12 months (Fig). About 25% of parents reported their children had daily consumption of at least one glass of formula milk until 6 years. There was no difference in family and birth characteristics by duration of regular formula-feeding.

Compared with participants who were exclusively breastfed at 0-3 months, those who were always formula-fed tended to have marginally higher total cholesterol, LDL cholesterol, triglycerides, and insulin resistance (Table 2). Exclusive breastfeeding

TABLE 1. Characteristics of participants by infant feeding mode at age 0-3 months and duration of formula-feeding

Characteristics	Infant feeding mode at age 0-3 months			Duration of formula-feeding, y		
	Exclusively breastfed (n=51)	Mixed (n=302)	Always formula-fed (n=344)	0-2 (n=316)	3-5 (n=183)	6 (n=183)
Male sex, %	31	47	44	47	42	42
Gestational age, %						
≤36 weeks	5.9	4.6	2.9	4.4	4.9	1.6
37-38 weeks	24	26	29	29	26	26
39-40 weeks	55	55	52	50	57	58
≥41 weeks	16	15	16	17	11	15
Gestational diabetes, %	8.2	7.9	11	8.6	8.4	11
Preeclampsia, %	2.0	3.2	4.5	3.4	3.6	2.9
Maternal smoking during pregnancy, %	0	1.4	5.6	3.3	4.0	3.4
Infant feeding during 0-3 months, %						
Always formula-fed	-	-	-	50	50	47
Mixed	-	-	-	43	45	43
Always breastfed	-	-	-	6.7	5.0	10
Infant growth, weight z-score						
At birth	-0.31	-0.32	-0.17	-0.22	-0.29	-0.25
At 3 months	0.29	0.06	0.13	0.10	0.07	0.13
At 12 months	-0.01	0.01	0.10	0.03	0.05	0.10
Parents' highest education, %						
9th grade or below	40	20	29	26	26	25
10th to 11th grade	32	39	49	43	41	46
12th grade or above	28	41	22	32	33	29
Hong Kong born mother, %	30	64	64	63	62	61
Hong Kong born father, %	48	75	72	69	76	74

at age 0-3 months had a graded association with lower fasting insulin (P value for trend=0.02) and lower insulin resistance (P value for trend=0.03). When we repeated the analyses (except for insulin resistance and hs-CRP) with an additional 1920 participants with blood tested at a similar age in another study, these associations with total cholesterol (*r*=0.19, 95% confidence interval [CI]= −0.04 to 0.41) and higher LDL cholesterol (*r*=0.12, 95% CI= −0.08 to 0.32) became significant. Body mass index and % body fat at age 17.5 years did not differ by infant feeding modes.

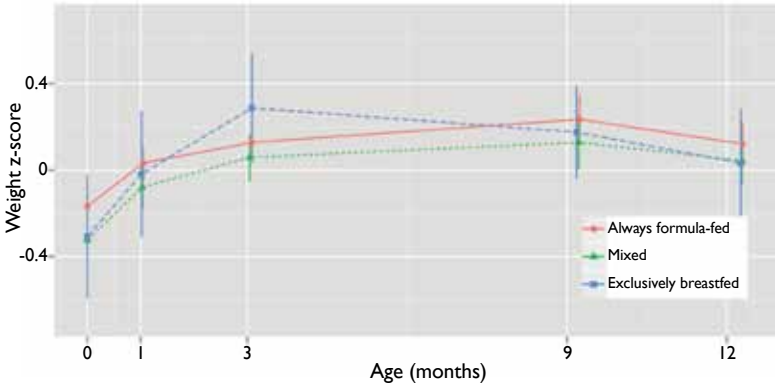


FIG. Weight z-score at age 0-12 months by infant feeding mode at age 0-3 months of life.

None of the above associations differed by sex or infant growth rate, and they were not attenuated after adjustment for infant growth (data not shown). The duration of formula-feeding was not associated with any risk factors of T2DM or other health markers at age 17.5 years (Table 2), with no interaction of sex (data not shown).

Discussion

Formula-feeding at 0-3 months was associated with higher LDL cholesterol but not associated with higher insulin resistance or adiposity markers at age 17.5 years. The lack of association between breastfeeding and adiposity in the present study and in the randomised controlled trial on breastfeeding promotion[2] is inconsistent with the protective effect of breastfeeding against obesity reported in some systematic reviews of observational studies.[3] Different social patterns on breastfeeding may result in various associations between infant feeding mode and subsequent adiposity in different stages of economic development. The null association of early infant feeding with adiposity at age 7 years and at young adulthood may be attributed to the lack of social patterns on breastfeeding in our population in the 1990s.

We also observed a null association of early infant feeding with fasting glucose levels. This is

TABLE 2. Adjusted associations of infant feeding mode at age 0-3 months and duration of formula-feeding with markers of health at age 17.5 years

	Value Mean±SD or median (range)		Infant feeding mode at age 0-3 months (β [95% CI])			Duration of formula-feeding, y (β [95% CI])		
	Male (n=315)	Female (n=395)	Exclusively breastfed	Mixed	Always formula-fed	0-1	3-5	6
Height, cm	172.1±6.0	159.6±5.4	Ref	−0.2 (−2.1 to 1.7)	0.1 (−1.7 to 1.9)	Ref	0.0 (−1.0 to 1.0)	0.2 (−0.8 to 1.3)
Body mass index, kg/m²	21.0±3.5	20.5±3.0	Ref	0.1 (−1.0 to 1.2)	0.1 (−1.0 to 1.1)	Ref	0.2 (−0.4 to 0.8)	−0.1 (−0.7 to 0.5)
Waist-to-height ratio z-score	0.43±0.05	0.43±0.04	Ref	0.0 (−0.3 to 0.3)	0.1 (−0.3 to 0.4)	Ref	0.0 (−0.1 to 0.2)	−0.1 (−0.3 to 0.1)
% body fat	15.1±5.8	27.7±5.5	Ref	0.2 (−1.7 to 2.1)	0.4 (−1.4 to 2.3)	Ref	−0.2 (−1.2 to 0.9)	−0.7 (−1.7 to 0.4)
Muscle mass, kg	49.7±6.2	35.2±3.2	Ref	−0.3 (−1.8 to 1.3)	−0.2 (−1.8 to 1.3)	Ref	0.8 (−0.1 to 1.6)	0.4 (−0.4 to 1.3)
Hand grip strength, kg	32.1±6.5	20.6±4.5	Ref	−0.4 (−2.2 to 1.5)	−0.7 (−2.5 to 1.1)	Ref	0.6 (−0.4 to 1.6)	0.7 (−0.3 to 1.7)
Haemoglobin A1c, %	5.4±0.2	5.4±0.2	Ref	−0.01 (−0.09 to 0.07)	−0.02 (−0.10 to 0.6)	Ref	0.01 (−0.03 to 0.05)	−0.04 (−0.08 to 0.01)
Fasting glucose, mmol/L	4.7±0.4	4.6±0.3	Ref	−0.08 (−0.19 to 0.04)	−0.07 (−0.18 to 0.05)	Ref	0.03 (−0.03 to 0.10)	0.01 (−0.06 to 0.08)
Fasting insulin, pmol/L*	63.7±28.1	60.0±36.1	Ref	0.02 (−0.04 to 0.08)	0.05 (−0.02 to 0.11)	Ref	−0.03 (−0.06 to 0.01)	−0.01 (−0.05 to 0.03)
Insulin resistance	1.09±0.65	1.16±0.51	Ref	0.03 (−0.17 to 0.22)	0.12 (−0.07 to 0.32)	Ref	−0.05 (−0.14 to 0.05)	−0.02 (−0.12 to 0.08)
Insulin sensitivity, % of homeostasis model assessment	115.1±53.9	101.9±44.8	Ref	−5.0 (−21.3 to 11.3)	−8.8 (−24.9 to 7.3)	Ref	6.9 (−2.1 to 15.8)	1.5 (−7.6 to 10.6)
Total cholesterol, mmol/L	3.9±0.7	4.1±0.7	Ref	0.19 (−0.03 to 0.42)	0.19 (−0.04 to 0.41)	Ref	−0.16 (−0.28 to −0.03)	−0.03 (−0.16 to 0.10)
Low-density lipoprotein cholesterol, mmol/L	2.0±0.6	2.2±0.6	Ref	0.15 (−0.05 to 0.35)	0.12 (−0.08 to 0.32)	Ref	−0.11 (−0.22 to 0.01)	0.01 (−0.11 to 0.12)
High-density lipoprotein cholesterol, mmol/L	1.4±0.3	1.6±0.3	Ref	0.06 (−0.05 to 0.17)	0.06 (−0.05 to 0.16)	Ref	−0.04 (−0.10 to 0.02)	−0.03 (−0.09 to 0.03)
Triglycerides, mmol/L	0.86±0.36	0.79±0.34	Ref	−0.00 (−0.12 to 0.11)	0.06 (−0.05 to 0.17)	Ref	−0.06 (−0.12 to 0.01)	−0.02 (−0.09 to 0.04)
High sensitive C-reactive protein, mg/dL*	0.03 (0.02-0.9)	0.03 (0.02-0.9)	Ref	−0.30 (−0.83 to 0.24)	−0.25 (−0.78 to 0.29)	Ref	0.23 (−0.07 to 0.53)	−0.10 (−0.40 to 0.21)

* Measured in 710 participants only; log-transformed value was used in regression analyses

consistent with findings from a meta-analysis of observational studies, which concluded that infant feeding has little effect on fasting glucose levels in adulthood.[3] Breastfed infants have a marginally lower insulin level and a significantly lower risk of T2DM in adulthood.[3] We observed associations between the always formula-fed participants and higher insulin resistance, and between exclusive breastfeeding at age 0-3 months and lower insulin resistance. However, these associations were not statistically significant, perhaps owing to the small sample size. Furthermore, we cannot rule out a delayed effect of early-life exposure on glucose metabolism that may only become obvious later in adulthood. Longer-term follow-up in a larger sample within the birth cohort are warranted to confirm the long-term effects of infant feeding on insulin resistance and glucose metabolism.

We found higher total and LDL cholesterol and marginally higher triglycerides among formula-fed participants. Systematic reviews have concluded that breastfeeding is associated with a modest reduction in total cholesterol in adulthood.[5] The literature on the association between breastfeeding and triglycerides is rather mixed. The association of formula-feeding with higher LDL cholesterol and triglycerides but not with adiposity indicates that different mechanisms may be involved. Breast milk contains higher cholesterol, and breastfed infants synthesised less cholesterol. It has been speculated that such change in homeostasis of cholesterol in early life may programme lipid profile in adulthood.

In the early 2000s, prolonged infant formula-feeding was common in Hong Kong, with 30% of our participants having daily consumption of infant formula at age 6 years. We did not observe any effects of duration of formula-feeding on any risk factor for T2DM or health markers at age 17.5 years. Prolonged formula-feeding may be a result of perceived poor growth or ill health. Therefore, 6-year-olds who did not receive infant formula may have been healthier or even overweight, suggesting a reverse causality in the association between prolonged formula-feeding and subsequent health.

There are some limitations to this study. We included only a subset of the birth cohort and participation in the follow-up was voluntary. However, breastfeeding was not socially patterned in the cohort, suggesting little residual confounding by unmeasured socio-economic status. Inverse probability weighting was used to mitigate any selection bias. Information on formula milk use provided by mothers was prone to recall bias. The societal value on prolonged formula-feeding was unclear, so there was unlikely any differential recall bias. Breastfeeding duration was commonly short in the 1990s in Hong Kong, which did not allow assessment on dose-response effect.

Conclusions

Compared with exclusive breastfeeding, formula-feeding at age 0-3 months was associated with poorer lipid profile and maybe greater insulin resistance but not associated with adiposity at age 17.5 years. Prolonged formula-feeding was unrelated to any markers of cardiovascular and metabolic health. Early infant nutrition may affect long-term health; exclusive breastfeeding, even for a short period, was associated with a healthier lipid profile. Our findings support the promotion of breastfeeding in Hong Kong. Further studies are warranted to assess the biological mechanisms by which breastfeeding duration affects health later in life.

Acknowledgements

This study was supported by the Health and Health Services Research Fund (HHSRF), Food and Health Bureau, Hong Kong SAR Government (#10111491). This work is a sub-study of the 'Children of 1997' birth cohort, which was initially supported by the Health Care and Promotion Fund, Health and Welfare Bureau, Hong Kong SAR Government (#216106) and re-established in 2005 with support from HHSRF (#03040771), and the University Research Committee Strategic Research Theme of Public Health, The University of Hong Kong. This sub-study builds on information added to the birth cohort supported by the Research Fund for the Control of Infectious Diseases, Food and Health Bureau, Hong Kong SAR Government (#04050172) and HHSRF (#08090761). The authors thank colleagues at the Student Health Service and Family Health Service of the Department of Health for their assistance and collaboration. The authors also thank the late Dr Connie O for coordinating the project and all the fieldwork for the initial study in 1997-8.

References

1. Singhal A, Fewtrell M, Cole TJ, Lucas A. Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. Lancet 2003;361:1089-97.
2. Martin RM, Patel R, Kramer MS, et al. Effects of promoting longer-term and exclusive breastfeeding on cardiometabolic risk factors at age 11.5 years: a cluster-randomized, controlled trial. Circulation 2014;129:321-9.
3. Owen CG, Martin RM, Whincup PH, Smith GD, Cook DG. Does breastfeeding influence risk of type 2 diabetes in later life? A quantitative analysis of published evidence. Am J Clin Nutr 2006;84:1043-54.
4. Schooling CM, Hui LL, Ho LM, Lam T.H., Leung GM. Cohort Profile: "Children of 1997": a Hong Kong Chinese birth cohort. Int J Epidemiol 2012;41:611-20.
5. Owen CG, Whincup PH, Kaye SJ, et al. Does initial breastfeeding lead to lower blood cholesterol in adult life? A quantitative review of the evidence. Am J Clin Nutr 2008;88:305-14.

Development and validation of a tool to identify barriers to starting insulin treatment in patients with type-2 diabetes mellitus

SN Fu*, WY Chin, CKH Wong, VTF Yeung, MP Yiu, HY Tsui, KH Chan

KEY MESSAGES

1. The 13-item Chinese version of the Attitudes to Starting Insulin Questionnaire has reliable psychometric properties and an interpretable and relevant structure. It can be used by clinicians to assess psychological barriers to insulin treatment in Chinese patients with type-2 diabetes mellitus in primary care settings.
2. The most significant barriers to starting insulin treatment in Chinese patients with poorly controlled type-2 diabetes mellitus appear to be fear of pain and needles and perceived insufficient social support. Women are more negative towards starting insulin treatment.

Hong Kong Med J 2018;24(Suppl 4):S24-9
HHSRF project number: 10112261

[1] SN Fu, [2] WY Chin, [2] CKH Wong, [3] VTF Yeung, [1] MP Yiu, [1] HY Tsui, [1] KH Chan

[1] *Department of Family Medicine & Primary Health Care, Kowloon West Cluster, Hospital Authority*
[2] *Department of Family Medicine & Primary Care, Li Ka Shing Faculty of Medicine, The University of Hong Kong*
[3] *Department of Medicine & Geriatrics, Our Lady of Maryknoll Hospital, Hospital Authority*

* Principal applicant and corresponding author: fusaunga@gmail.com

Introduction

In Hong Kong, type-2 diabetes mellitus (T2DM) is commonly managed in general out-patient clinics. Insulin treatment is eventually indicated once the maximal dose of oral medication is no longer sufficient to control the blood sugar level ('failed oral therapy'). Most patients with T2DM resist insulin treatment,[1] particularly Chinese patients (>70%),[2] women, and patients with lower education levels,[3] probably owing to cognitive appraisals or emotional reactions affected by culture, degree of self-efficacy, and health literacy.[1]

None of the existing questionnaires[4,5] have been validated for use in predominantly elderly or socially deprived primary care patients who have not yet started insulin treatment ('insulin naïve' patients). This study aimed (1) to develop a Chinese questionnaire and to assess its psychometric properties, acceptability, and feasibility in elderly patients with T2DM in primary care settings; and (2) to determine the association between attitude toward starting insulin treatment and biomedical and socio-demographic factors in patients with poorly controlled T2DM who were receiving the maximum tolerable dose of oral drugs.

Methods

This study was approved by the Research Ethics Committee of the Kowloon West Cluster, Hospital Authority of Hong Kong.

A total of 27 potential items were identified from a literature review.[1,2,4,5] An expert panel rated the items for content, breadth, validity, and relevancy. Each item that scored ≥80% on the content validity index was retained. The resulting structured English questionnaire used a four-point Likert scale for each item (from strongly agree to strongly disagree). The questionnaire was translated into Chinese and back-translated into English. The resulting Chinese version of the Attitudes to Starting Insulin Questionnaire (Ch-ASIQ) was field tested in 10 patients with different age, sex, and previous insulin use status.

Consecutive eligible patients were identified through the Hospital Authority system and invited to complete the questionnaire by self-administration or face-to-face interview from June 2012 to March 2013. There were 27 potential items; therefore, a sample size of 270 was required for a patient-to-item ratio of 10:1. The inclusion criteria were (1) Chinese-speaking adults aged ≥18 and ≤80 years, (2) receiving the maximum recommended or tolerable doses of oral diabetic medications (gliclazide 320 mg, modified release gliclazide 120 mg, or glibenclamide 15 mg and metformin ≥2 g daily), and (3) haemoglobin A1c level of ≥7.5% within the past 12 months. Exclusion criteria were pregnancy, inability to answer the questionnaire, and already receiving insulin treatment.

Under the Risk Factor Assessment and Management Programme, patients with T2DM underwent laboratory tests, retinal photo or ophthalmologist assessment, and nurse-led diabetes

complication screening once every 1 to 2 years. Our nurses collected the patients' records for data analysis.

Negative items were reverse coded. Scores ranged from one to four, with higher scores indicating more positive attitudes. Exploratory factor analysis was used to explore the instrument's underlying structure and to sort the items into subscales. The Kaiser-Meyer-Olkin measure of sampling adequacy (using a cut-off of 0.5) and Bartlett's Test of Sphericity (using a cut-off P<0.001) were used to ensure the appropriateness of the dataset for exploratory factor analysis. A Cronbach's alpha coefficient of ≥0.6 was used as the cut-off to indicate

TABLE 1. Sociodemographic and clinical characteristics of patients with type-2 diabetes mellitus

Characteristics	Mean (range) or No. (%) of patients (n=303)
Age, y	63 (54-70)
Male	136 (44.9)
Female	167 (55.1)
Education	
No formal education	44 (15.4)
Primary	117 (41.1)
Secondary	107 (37.5)
Tertiary	17 (6.0)
Occupation	
Full-time	90 (32.8)
Unemployed/retired	82 (29.9)
Homemaker	99 (36.1)
Part-time	3 (1.1)
Mode of questionnaire administration	
Self	104 (34.4)
Interviewer	199 (65.7)
Duration of diabetes mellitus, y	11 (7-16)
Diabetes drug	
Glibenclamide	37 (12.2)
Gliclazide	259 (85.5)
Metformin	7 (2.3)
Body mass index, kg/m^2	25.2 (22.6-27.7)
Body mass index cut-off, kg/m^2	
<18.50 (underweight)	3 (1.0)
≥18.50 to <24 (normal)	109 (36.5)
≥24 to <27 (overweight)	91 (30.4)
≥27 (obese)	96 (32.1)
Haemoglobin A1c level, %	8.3 (7.9-9.1)
Low-density lipoprotein, mmol/L	2.5 (2.0-3.0)
Estimated glomerular filtration rate, mL/min/1.73m^2	88.0 (70.5-108.0)
Hypertension	246 (81.2)
Nephropathy	49 (16.8)
Foot ulcer	4 (1.4)
Neuropathy	6 (2.0)
Peripheral vascular disease	0 (0.0)
Retinopathy	165 (57.5)
Ischaemic heart disease	5 (1.7)
Stroke	14 (4.8)

sufficient internal reliability. Linear regression was performed to explore the associations of Ch-ASIQ with socio-demographic and clinical characteristics. SPSS (version 20.0; IBM Corp., Armonk [NY], US) was used for statistical analyses.

Results

All 27 items yielded >80% on the content validity index and cognitive debriefing. Of the 306 patients invited, 303 completed the questionnaire (response rate, 99%). The median haemoglobin A1c level was 8.3% (interquartile range, 7.9%-9.1%) indicating very poor glycaemic control (Table 1).

Ten factors with eigenvalues of ≥1 were extracted using exploratory factor analysis with varimax rotation. The Kaiser-Meyer-Olkin measure was 0.725, indicating sampling adequacy. Sufficient variability of data was confirmed by Bartlett's Test of Sphericity (P<0.001).

After collapsing and combining factors, the internal consistency of four out of the seven subscales had Cronbach's alpha values of >0.6, indicating sufficient internal consistency (Table 2). The remaining subscales had poor internal consistency were removed.

The final instrument yielded 13 items in four subscales: (1) self-image and stigmatisation, (2) factors promoting self-efficacy, (3) fear of pain or needles, and (4) time and family support.

The mean scores of the 13 items of the Ch-ASIQ were calculated. The mean overall Ch-ASIQ score was 2.50 (standard deviation, 0.38), which was the mid-point. The item yielding the most negative attitude toward starting insulin treatment was "I am afraid of needle injection" (70.6%), whereas the item yielding the most positive attitude towards starting insulin treatment was "I can manage the skill of injecting insulin" (67.5%) in the factors promoting self-efficacy subscale.

The linear regression analysis showed that women had more negative attitudes toward starting insulin treatment (P=0.022, Table 3). Patients who could not self-administer the questionnaire had lower scores on the factors promoting self-efficacy subscale. Age, education level, working status, haemoglobin A1c, coexisting hypertension, and complications related to retinopathy were not associated with the Ch-ASIQ scores.

Discussion

Two subscales of the Ch-ASIQ measure two common psychological barriers to starting insulin treatment: stigma of insulin use and fear of injection. Clinicians should consider patients' negative emotions and concerns when counselling them to start insulin treatment. Similarly, two subscales of the Ch-ASIQ measure patients' perceived needs in terms of personal resources required to take on the added responsibility of insulin therapy. It is important to identify ways to empower patients, especially those with lower education levels and health literacy, and to assess their needs in terms of knowledge, skills, and social support. Time should be factored in an evaluation of a patient's readiness to adhere to any change in drug regimen.

Time appears to be an important factor, although less than one-third of the patients were employed full-time. This may reflect long working hours and limited free time.

The deleted items 'Misunderstanding of insulin therapy', 'Worry about complications of insulin therapy', and 'Trust in health care professionals' appear to be relatively unimportant in our study population, possibly owing to their lower levels of education, age, and ethnicity. Elderly Chinese patients appear to be less likely to question the doctor's expertise or advice.

The items related to fear of hypoglycaemia, weight gain, and complications of insulin, which have been reported to be important,[4,5] were not consistently weighted in the exploratory factor analysis on our patients. Similar findings were also found in another study that interviewed Chinese subjects.[2] One explanation is that the anxiety evoked by injection exceeds that evoked by any other factor.

One reason for insulin refusal is that Chinese patients might not trust Western medicine.[1] Nonetheless, in our patients, the items related to distrust of Western medicine were deleted, indicating that these were not barriers to starting insulin treatment in our patients.

The mean overall score for attitudes toward insulin treatment was at the mid-point (2.5), indicating ambivalence. Fear of pain and needles has been reported to be an important barrier to starting insulin treatment.[1-3] Primary healthcare professionals should be trained to manage patients' anxiety about needles, counsel patients on the use of less-painful insulin pens, instruct patients on proper injection techniques, and provide support to help patients starting insulin treatment.

There are limitations to the study. The questionnaire was interviewer-administered in most patients owing to poor literacy levels. The psychometric properties of the Ch-ASIQ may have differed if self-administered. Test-retest reliability measurements were not performed; further studies to examine the responsiveness of the instrument (ability to detect change) following intervention or over time are warranted. Our patients were generally older; younger patients with higher education levels might have responded differently. Further studies with age subgroups are needed.

TABLE 2. Mean scores of individual items and internal consistency of each subscale

Subscale/item	Mean±standard deviation score	No. (%) of patients agree/totally agree	Cronbach's alpha if item deleted
Self-image and stigmatisation (Cronbach's alpha=0.802)			
Item 22: I worry that people will know I have diabetes if I am on insulin treatment	2.36±0.85	121 (40.33)	0.702
Item 23: Injecting insulin is embarrassing; I worry about being seen when I inject insulin	2.49±0.81	147 (49.16)	0.663
Item 24: If I have to inject insulin, it makes me feel like a drug addict	2.45±0.80	133 (44.93)	0.812
Factors promoting self-efficacy (Cronbach's alpha=0.675)			
Item 1: I have up-to-date knowledge about diabetes management	2.60±0.83	189 (63.21)	0.670
Item 8: Insulin can help control blood glucose and prevent complications	2.65±0.68	181 (63.73)	0.618
Item 14: I can manage the skill of injecting insulin	2.72±0.75	201 (67.45)	0.592
Item 26: There is social support available if I have to inject insulin	2.37±0.68	131 (44.41)	0.601
Item 27: I can pay as close attention to my diet as insulin treatment requires. For example, I may need to eat snacks or reduce my amount of eating accordingly.	2.67±0.66	196 (66.67)	0.640
Fear of pain or needles (Cronbach's alpha=0.653)			
Item 13: Injecting insulin is painful	2.79±0.73	200 (66.89)	0.620
Item 16: I am afraid of needle injections	2.91±0.86	211 (70.57)	0.340
Item 17: I worry about needing to perform home blood sugar monitoring	2.59±0.82	158 (53.02)	0.656
Time and family support (Cronbach's alpha=0.620)			
Item 20: I can spare enough time to perform insulin injection	2.58±0.71	176 (59.46)	-
Item 25: My family will support me in injecting insulin	2.45±0.73	133 (45.70)	-
Misunderstanding of insulin therapy (Cronbach's alpha=0.573)			
Item 6: Insulin can cause permanent damage to or worsening of my health	2.50±0.71	133 (45.86)	0.512
Item 9: Diabetes tablets work better than insulin	2.82±0.70	205 (69.26)	0.460
Item 10: Insulin injection means failure of oral diabetes treatment	2.73±0.64	197 (66.55)	0.560
Item 15: Injecting insulin is inconvenient	3.05±0.72	242 (80.40)	0.463
Worry about complications of insulin therapy (Cronbach's alpha=0.488)			
Item 5: Insulin treatment for diabetes causes feelings of drug dependence	2.63±0.69	172 (58.70)	0.550
Item 11: An insulin overdose can lead to extremely low blood sugar levels (hypoglycaemia). I am afraid of experiencing the symptoms of low blood sugar levels.	2.61±0.68	168 (57.53)	0.337
Item 12: I worry about weight gain associated with insulin injections	2.40±0.65	117 (39.80)	0.374
Item 18: I worry about skin marks or skin complications associated with injecting insulin	2.56±0.72	152 (51.18)	0.383
Item 21: Insulin treatment will make life less flexible or affect my social life and hobbies (eg, performing exercise, dining out)	2.67±0.73	174 (58.78)	0.485
Trust in health care professionals (Cronbach's alpha=0.203)			
Item 2: I trust that my doctor is providing me with the most appropriate diabetes management for me	3.22±0.60	278 (92.67)	-
Item 3: I wish to or I am now trying traditional Chinese medicine to control blood sugar	2.35±0.79	130 (43.05)	-
Item 4: I wish to or am now trying lifestyle (diet control and exercise) or other alternative medicine (eg, complementary medicine, Qi Kung, etc) to control blood sugar	3.15±0.58	280 (92.72)	-

TABLE 3. Factors associated with the Chinese version of the Attitudes to Starting Insulin Questionnaire

Factors	Self-image and stigmatisation*		Factors promoting self-efficacy†	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Age	–0.006 (–0.018 to 0.006)	0.359	–0.007 (–0.015 to 0.002)	0.114
Female	0.158 (–0.058 to 0.374)	0.152	–0.083 (–0.238 to 0.073)	0.297
Education				
No formal education		0.568		0.277
Secondary or above	0.127 (–0.154 to 0.408)	0.376	0.164 (–0.039 to 0.367)	0.112
Primary	0.037 (–0.227 to 0.301)	0.783	0.102 (–0.087 to 0.291)	0.290
Working status				
Working		0.427		0.993
Homemaker	–0.130 (–0.389 to 0.128)	0.324	–0.009 (–0.193 to 0.175)	0.924
Unemployed/retired	–0.152 (–0.397 to 0.093)	0.223	–0.009 (–0.184 to 0.165)	0.919
Interviewer administration	0.063 (–0.117 to 0.244)	0.491	–0.176 (–0.303 to –0.049)	0.007
Duration of diabetes	–0.012 (–0.027 to 0.004)	0.140	0.007 (–0.004 to 0.017)	0.225
Diabetes drug				
Metformin only		0.152		0.187
Gliclazide and metformin	–0.482 (–0.983 to 0.018)	0.059	0.330 (–0.036 to 0.696)	0.078
Glibenclamide and metformin	–0.527 (–1.078 to 0.024)	0.061	0.271 (–0.128 to 0.671)	0.183
Body mass index				
Underweight/normal		0.195		0.359
Overweight	–0.088 (–0.299 to 0.123)	0.414	–0.108 (–0.258 to 0.043)	0.160
Obese	–0.199 (–0.415 to 0.017)	0.071	–0.038 (–0.191 to 0.115)	0.624
Haemoglobin A1c	–0.028 (–0.103 to 0.048)	0.473	0.046 (–0.008 to 0.099)	0.095
Low-density lipoprotein	–0.073 (–0.186 to 0.040)	0.204	0.023 (–0.054 to 0.101)	0.552
Estimated glomerular filtration rate	0.001 (–0.003 to 0.005)	0.501	0.002 (–0.001 to 0.005)	0.195
Hypertension	0.142 (–0.076 to 0.360)	0.203	0.093 (–0.064 to 0.250)	0.248
Nephropathy	0.247 (–0.025 to 0.519)	0.075	0.034 (–0.154 to 0.223)	0.721
Retinopathy	0.079 (–0.094 to 0.252)	0.370	0.048 (–0.074 to 0.171)	0.439

* Higher scores indicate greater barriers to insulin treatment
† Higher scores indicate lower barriers to insulin treatment

Conclusions

The 13-item Chinese version of Ch-ASIQ has reliable psychometric properties and an interpretable and relevant structure. The most significant barriers to starting insulin treatment appear to be fear of pain and needles and perceived insufficient social support. Nonetheless, most patients are aware of the effectiveness of insulin and have confidence to learn the skill of insulin injection. Women are more negative towards starting insulin treatment and have more fear of pain and needles. Support and education for patients may increase their acceptance of insulin treatment.

Acknowledgements

This study was supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (#10112261). The authors thank all of the nursing staff, family physicians, and consultants for their support, especially Service Director Dr Wong Tak Cheung and Chief of Service Dr Yiu Yuk Kwan of the Department of Family Medicine and Primary Health Care, Kowloon West Cluster, Hospital Authority. The authors also express special thanks to volunteer student helpers Ms TC Ip, Ms T Shiu, and Mr SW Chau.

References

1. Wang HF, Yeh MC. Psychological resistance to insulin therapy in adults with type 2 diabetes: mixed-method systematic review. J Adv Nurs 2012;68:743-57.
2. Wong S, Lee J, Ko Y, Chong MF, Lam CK, Tang WE.

Fear of pain or needles*		Time and family support†		Overall*	
Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
–0.003 (–0.014 to 0.008)	0.550	–0.001 (–0.013 to 0.011)	0.868	0.002 (–0.005 to 0.009)	0.633
0.266 (0.068 to 0.465)	0.008	–0.054 (–0.261 to 0.154)	0.611	0.154 (0.022 to 0.285)	0.022
	0.909		0.398		0.827
0.046 (–0.209 to 0.300)	0.725	0.167 (–0.101 to 0.435)	0.221	–0.050 (–0.221 to 0.122)	0.569
0.053 (–0.185 to 0.290)	0.664	0.166 (–0.084 to 0.416)	0.192	–0.048 (–0.208 to 0.112)	0.558
	0.428		0.227		0.799
0.124 (–0.114 to 0.362)	0.307	0.150 (–0.101 to 0.401)	0.241	–0.024 (–0.181 to 0.134)	0.769
0.136 (–0.086 to 0.359)	0.230	0.204 (–0.035 to 0.443)	0.094	–0.050 (–0.198 to 0.097)	0.503
0.125 (–0.042 to 0.291)	0.141	0.057 (–0.116 to 0.230)	0.518	0.103 (–0.004 to 0.210)	0.060
0.002 (–0.012 to 0.016)	0.756	0.004 (–0.011 to 0.019)	0.592	–0.006 (–0.015 to 0.003)	0.178
	0.087		0.960		0.063
–0.365 (–0.818 to 0.089)	0.115	–0.065 (–0.536 to 0.406)	0.786	–0.360 (–0.663 to –0.057)	0.020
–0.162 (–0.662 to 0.337)	0.524	–0.074 (–0.596 to 0.447)	0.780	–0.320 (–0.651 to 0.012)	0.059
	0.459		0.073		0.628
–0.112 (–0.306 to 0.082)	0.256	0.235 (0.032 to 0.437)	0.023	–0.022 (–0.148 to 0.104)	0.733
–0.105 (–0.303 to 0.094)	0.301	0.102 (–0.105 to 0.309)	0.336	–0.063 (–0.193 to 0.067)	0.342
–0.039 (–0.110 to 0.031)	0.275	0.038 (–0.036 to 0.111)	0.316	–0.042 (–0.086 to 0.003)	0.070
–0.043 (–0.147 to 0.061)	0.414	0.050 (–0.056 to 0.156)	0.351	–0.059 (–0.124 to 0.007)	0.082
0.001 (–0.003 to 0.004)	0.762	0.001 (–0.002 to 0.005)	0.503	–0.001 (–0.003 to 0.002)	0.671
–0.012 (–0.215 to 0.191)	0.909	–0.016 (–0.227 to 0.194)	0.879	–0.026 (–0.160 to 0.108)	0.701
0.307 (0.062 to 0.552)	0.014	–0.070 (–0.327 to 0.186)	0.590	0.120 (–0.036 to 0.277)	0.132
0.093 (–0.065 to 0.251)	0.251	0.043 (–0.123 to 0.208)	0.611	0.023 (–0.079 to 0.126)	0.655

Perceptions of insulin therapy amongst Asian patients with diabetes in Singapore. Diabet Med 2011;28:206-11.
3. Nam S, Chesla C, Stotts NA, Kroon L, Janson SL. Factors associated with psychological insulin resistance in individuals with type 2 diabetes. Diabetes Care 2010;33:1747-9.
4. Petrak F, Stridde E, Leverkus F, Crispin AA, Forst T, Pfutzner A. Development and validation of a new measure to evaluate psychological resistance to insulin treatment. Diabetes Care 2007;30:2199-204.
5. Snoek FJ, Skovlund SE, Pouwer F. Development and validation of the insulin treatment appraisal scale (ITAS) in patients with type 2 diabetes. Health Qual Life Outcomes 2007;5:69.

Environmental risk factors of prostate cancer: a case-control study

LA Tse*, WM Ho, F Wang, YH He, CF Ng

KEY MESSAGES

1. This study provides the first epidemiological evidence on the link between chronic bisphenol A (BPA) exposure and prostate cancer risk.
2. Policies to remove toxicant BPA at source should be implemented to ameliorate prostate cancer risk. Personalised education programmes should be implemented to modify unhealthy dietary habits and avoid hazardous working schedules that disrupt the circadian rhythm.
3. The validated assessment tool can be used as a reasonable reference in the Hong Kong population to identify potential sources of BPA exposure via the route of ingestion and evaluate the exposure level in daily living.

Hong Kong Med J 2018;24(Suppl 4):S30-3
HMRF project number: 11121091

[1] LA Tse, [2] WM Ho, [1] F Wang, [3] YH He, [4] CF Ng

[1] *Division of Occupational and Environmental Health, Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong*
[2] *Department of Clinical Oncology, Prince of Wales Hospital*
[3] *Guilin Medical College, Guangxi Province, China*
[4] *SH Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong*

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

Introduction

Advancing age, race, and family history of prostate cancer are established risk factors of prostate cancer.[1] The influence of environmental factors on prostate cancer aetiology remains unclear. Geographic variations in age-standardised incidence of prostate cancer have been positively correlated to detection rates of urinary bisphenol A (BPA). Oestrogen-like BPA has been linked to prostate cancer risk in animals, but evidence for this link in humans is scarce. There is no information on environmental exposure and prostate cancer aetiology in a Hong Kong population. The aim of the present study was to document the association between environmental exposure to BPA and the risk of prostate cancer among Hong Kong Chinese men, and to examine the exposure-response relationship between cumulative BPA exposure index and prostate cancer risk.

Methods

This case-control study was conducted between August 2011 and November 2016. Consecutive Chinese men aged 35 to 84 years who were diagnosed with primary prostate cancer (ICD-10 code C61) by histology were recruited from the Department of Surgery and Clinical Oncology of a regional hospital. Controls were selected at random from patients being treated at the same hospital for diseases other than prostate cancer or benign prostate hyperplasia (BPH). We also recruited a total of 855 patients with biopsy-confirmed BPH; they were likely biased controls, as they may share some common exposure with the cases. Therefore, comparisons were based mainly on cases with prostate cancer and controls without BPH; patients with BPH were used only as supporting data.

Participants were interviewed by trained staff using a standardised questionnaire that covered information on education level, smoking habit, alcohol drinking, dietary habit, supplement intake, physical activity, history of benign disease in genitourinary system, family cancer history of first-degree relatives, occupation, shift work, and environmental exposure to BPA. Diagnostic and histological data were extracted from hospital records.

A new tool to assess environmental BPA exposure was developed, based on a literature review, to reconstruct each participant's past exposure to BPA according to a master list of food or beverage containers under different handling processes. The assessment tool was further validated by two experts in environmental hygiene and food safety who blindly rated the exposure intensity of BPA based on the same master list and same rating scale. High inter-rater and inter-method agreement on interclass correlation coefficient was achieved, indicating good replication and validation of the new assessment tool for evaluation of BPA exposure (Table 1). A novel cumulative BPA exposure index was constructed based on a standard approach commonly used in assessing hazardous substances in workplace environment: multiplying the square of exposure score by the frequency (per week) and years of use for each type of container under a specific handling practice, and then summed over all types of containers in a lifetime.

Risk factors between cases and controls were compared using Chi square or Student's *t* tests. Multiple logistic regression analysis was performed to determine odds ratio (OR) and 95% confidence interval (CI). An exposure-response relationship was considered significant when a P value for trend was <0.05.

Results

Cases (n=431) and controls (n=402) were comparable in terms of age at diagnosis (69.4 vs 68.2 years). More cases than controls were married (P=0.039) or retired (P=0.046) [Table 2]. Among potential risk factors of prostate cancer in Hong Kong Chinese men, family history of prostate cancer was more common in cases than controls (9.5% vs 3.0%, P<0.001, Table 3), with an adjusted OR of 3.68 (95% CI=1.85-7.34). Weekly consumption of deep-fried food and pickled vegetables was associated with an increased risk of prostate cancer by 85% (95% CI=15%-195%) and 87% (95% CI=7%-228%), respectively. Night shift work was hazardous (OR=1.76, 95% CI=1.07-2.89), but habitual green tea drinking was protective (OR=0.56, 95% CI=0.34-0.91). A positive exposure-response relationship between cumulative BPA exposure index and prostate cancer was observed, with a more prominent gradient in men under the age of 70 years. The use of commercial food containers was positively related to prostate cancer risk, but only habitual drinking of chilled water in a plastic container showed a significant association.

TABLE 1. Intraclass correlation coefficient for the inter-method and inter-rater agreement on bisphenol A exposure

Master list of environmental bisphenol A exposure	Literature review	Intraclass correlation coefficient (95% confidence interval)*	
		Expert 1	Expert 2
Including all items			
Literature review	1.00	0.90 (0.81-0.95)	0.86 (0.73-0.93)
Expert 1		1.00	0.94 (0.88-0.97)
Expert 2			1.00
Excluding items of glass or metal			
Literature review	1.00	0.87 (0.71-0.85)	0.82 (0.58-0.92)
Expert 1		1.00	0.92 (0.82-0.97)
Expert 2			1.00

* Coefficient of <0.40, 0.40-0.75, and >0.75 is interpreted as poor, moderate-to-good, and excellent agreement, respectively

TABLE 2. Sociodemographic variables of prostate cancer cases and hospital controls

Variable	Cases (n=431)*	Controls (n=402)*	P value
Age, y	69.4±7.3	68.2±8.2	0.027
Education			0.562
Primary or below	177 (41.1)	157 (39.1)	
Secondary school	197 (45.7)	198 (49.2)	
College or above	57 (13.2)	47 (11.7)	
Place of birth			0.481
Hong Kong	161 (37.3)	167 (41.6)	
Mainland China	249 (57.8)	216 (53.7)	
Southeast Asia	21 (4.9)	19 (4.7)	
Marital status			0.039
Married	400 (92.8)	352 (87.5)	
Widower	14 (3.3)	24 (6.0)	
Single or divorced	17 (3.9)	26 (6.5)	
Retirement status			0.046
Retired	329 (76.3)	286 (71.1)	
Employed	102 (23.7)	116 (28.9)	

* Data are presented as mean ± standard deviation or No. (%) of patients

Discussion

Our study found that some dietary habits, night shift work, and environmental BPA exposure are risk factors of prostate cancer among Hong Kong Chinese men. Prostate cancer was positively associated with consumption of deep-fried food and pickled vegetables, independent of other risk factors or confounders. Deep-fried food has high levels of heterocyclic amines and other mutagens/carcinogens. The carcinogenic effect of preserved food on prostate cells may be related to some mutagenic activities in pickled vegetables (mustard greens). An inverse association of prostate cancer with habitual green tea intake may be related to epigallocatechin 3-gallate, which is a potent catechin that specifically inhibits carcinogenesis of prostate cells.

According to the International Agency for Research on Cancer in 2007, shift work that disrupts the circadian rhythm is probably carcinogenic to humans (Group 2A).[2] Night shift work may lead to sustained low levels of melatonin, increasing prostate cancer risk. Sleep deprivation secondary to night shift work increases the pro-inflammatory response process but decreases the immune defence against free radicals, thus increasing the carcinogenesis process.[3]

In 2014, evidence of a direct link between BPA exposure and human prostate cancer was first reported.[4,5] Abnormalities of centrosome (a hallmark of malignant transformation) induced by low levels of BPA were highlighted as the potential mechanism in promoting the formation of prostate cancer.[5] Our study provides the first epidemiological evidence that cumulative exposure to BPA is associated with an increased risk of prostate cancer in a Chinese population. In addition, an exposure-response relationship was observed among Chinese men aged

TABLE 3. Potential risk factors of prostate cancer in Hong Kong Chinese men

Variables	Prevalence*		P value	Main effect model	Full model
	Cases (n=431)	Controls (n=402)		Adjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Family prostate cancer history			<0.001		
Negative	390 (90.5)	390 (97.0)		1.00	1.00
Positive	41 (9.5)	12 (3.0)		3.54 (1.81-6.95)	3.68 (1.85-7.34)
Deep-fried food consumption			<0.001		
<1 time per month	208 (48.3)	210 (52.2)		1.00	1.00
1-3 times per month	137 (31.8)	152 (37.8)		1.03 (0.75-1.41)	0.91 (0.65-1.27)
≥1 time per week	86 (20.0)	40 (10.0)		2.36 (1.51-3.68)	1.85 (1.15-2.95)
Pickled vegetables consumption			0.006		
<1 time per month	204 (47.3)	199 (49.5)		1.00	1.00
1-3 times per month	175 (40.6)	180 (44.8)		0.95 (0.74-1.28)	0.90 (0.66-1.23)
≥1 time per week	52 (12.1)	23 (5.7)		2.24 (1.31-3.84)	1.87 (1.07-3.28)
Green Tea drinking habit			0.040		
Non-habitual	396 (91.9)	351 (87.3)		1.00	1.00
Habitual	35 (8.1)	51 (12.7)		0.60 (0.387-0.96)	0.56 (0.34-0.91)
Nightshift work			0.005		
Never	366 (84.9)	372 (92.5)		1.00	1.00
Ever	58 (13.5)	30 (7.5)		1.87 (1.16-3.01)	1.76 (1.07-2.89)
Cumulative bisphenol A index					
All participants			0.018		
Low	75 (17.4)	101 (25.1)		1.00	1.00
Middle	232 (53.8)	201 (50.0)		1.66 (1.15-2.40)	1.54 (1.05-2.26)
High	124 (28.8)	100 (24.9)		1.88 (1.24-2.86)	1.57 (1.01-2.44)
P value for trend				0.014	0.057
Participants aged <70 years			0.048		
Low	40 (16.7)	61 (24.8)		1.00	1.00
Middle	123 (51.5)	124 (50.4)		1.62 (0.99-2.64)	1.56 (0.94-2.59)
High	76 (31.8)	61 (24.8)		2.10 (1.22-3.64)	1.79 (1.01-3.18)
P value for trend				0.017	0.056

* Data are presented as No. (%) of patients

>70 years who were born around or prior to the time BPA was introduced in the industrialised world. This correlation suggests a potential influence of early exposure in the development of prostate cancer. Although only habitually drinking chilled water in a plastic container was identified as a significant risk factor, there is a positive association between other types of commercial food or beverage containers and prostate cancer risk.

There are limitations to the study. Several factors might generate biases. Selection bias is a concern as all cases were recruited from a single centre. Nonetheless, the age distribution of our cases was similar to that from the Hong Kong Cancer Registry. Using hospital patients as controls may be a concern, as their lifestyle habits may differ from those of the general population. However, hospital controls with diverse diagnoses may reduce the potential selection bias, but the response rate of hospital controls was higher than that of healthy controls from the general population. Cumulative BPA exposure index is regarded as the best available indicator for chronic BPA exposure by ingestion because it is generally infeasible for case-control studies to have bio-monitoring data. Hence, capture of reliable chronic exposure to BPA has to rely on a well-designed questionnaire covering long-term exposure. We developed and validated a new assessment tool to evaluate chronic BPA exposure, with the collective index representing the chronic

exposure to environmental BPA via ingestion. Although BPA may also enter into human body via direct contact or inhalation, routes other than ingestion cannot be totally ignored. Misclassification of BPA exposure is a concern, as we did not consider exposure variations over time. This possible recall bias may be non-differential misclassification, which in turn lead to a potential underestimation of the association between cumulative BPA exposure index and prostate cancer, partly because the use of BPA in food and water containers has recently declined. Our sample is relatively small and has limited power to determine in-depth associations of specific type of food container under different handling process. Only 855 biopsy-negative controls (rather than the estimated 1200) were eventually obtained when we recruited 431 'true cases'. Further evidence from multiple logistic regression analysis for the 855 patients with BPH and 401 controls without BPH showed a greater gradient between cumulative BPA exposure index and BPH (adjusted ORs for the low, middle, and high cumulative BPA exposure index were 1.00, 2.08, and 2.55, respectively) than that was observed between cumulative BPA exposure index and prostate cancer. As BPH and prostate cancer may share some risk factors, any association between BPA and prostate cancer is likely to be biased if the patients with BPH were used as the controls.

Conclusions

Among Hong Kong Chinese men, risk factors of prostate cancer are family history of prostate cancer, night shift work, and frequent consumption of deep-fried food and pickled vegetables, whereas habitual green tea drinking has a moderately beneficial effect. Chronic exposure to environmental BPA is associated with an elevated prostate cancer risk, in particular for those with prostate cancer occurred below the age of 70 years. Frequent drinking of chilled water from a plastic container is the most significant source of environmental BPA by ingestion. Policies to remove the toxicant BPA at source should be implemented to ameliorate the prostate cancer risk. Personalised education programmes are recommended to promote healthy dietary habits and avoid hazardous working schedules. The newly developed assessment tool can be used as a reference in Hong Kong populations to help understand potential sources and exposure levels of environmental BPA by ingestion.

Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#11121091). The authors thank the following for their helpful advice and support: Dr Lam Tsan Augustine, Dr Lee Man Kei, Ms Law Ka Wai, Ms Lau Fung Ching Elsa, Ms Chan Wah Mui Virene, Mr Steven Leung, Ms Wong Lai Hung, Family Medicine Training Centre, Prince of Wales Hospital; Prof Ng Siu Man Simon, Department of Surgery, Prince of Wales Hospital; Miss Yip Siu Ying Jenny and Miss Lau Sui Yan Becky, Division of Urology, The Chinese University of Hong Kong; Miss Lee Ming Yi Priscilla, Miss Tsoi Hiu Man Tess, and Miss Kwok Ho Ling Bonnie, JC School of Public Health and Primary Care, The Chinese University of Hong Kong; Prof Jenifer C Hartle, Department of Health Science and Recreation, San Jose State University; and Prof Leung Ka-sing, Department of Applied Biology and Chemical Technology, Hong Kong Polytechnic University. The authors also thank the patients and staff of the departments of oncology and surgery for their support.

Results of this study have been published in: Tse LA, Lee PM, Ho WM, et al. Bisphenol A and other environmental risk factors for prostate cancer in Hong Kong. Environ Int 2017;107:1-7.

References

1. Hsing AW, Chokkalingam AP. Prostate cancer epidemiology. Front Biosci 2006;11:1388-413.
2. Straif K, Baan R, Grosse Y, et al. Carcinogenicity of shift-work, painting, and fire-fighting. Lancet Oncol 2007;8:1065-6.
3. Faraut B, Bayon V, Leger D. Neuroendocrine, immune and oxidative stress in shift workers. Sleep Med Rev 2013;17:433-44.
4. Prins GS, Hu WY, Shi GB, et al. Bisphenol A promotes human prostate stem-progenitor cell self-renewal and increases in vivo carcinogenesis in human prostate epithelium. Endocrinology 2014;155:805-17.
5. Tarapore P, Ying J, Ouyang B, Burke B, Bracken B, Ho SM. Exposure to bisphenol A correlates with early-onset prostate cancer and promotes centrosome amplification and anchorage-independent growth in vitro. PLoS One 2014;9:e90332.

Predictive biomarkers for EGFR tyrosine kinase inhibitors in treatment of advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomised controlled trials

ZY Yang, C Mao*, DY Zheng, JL Tang

KEY MESSAGES

1. Of the four potential predictive biomarkers studied, epidermal growth factor receptor (*EGFR*) gene mutations are the most powerful predictor of the efficacy of EGFR tyrosine kinase inhibitors in advanced non-small-cell lung cancer. They should be tested prior to treatment to select patients who are more likely to benefit from EGFR tyrosine kinase inhibitors.
2. Chemotherapy is a better choice than EGFR tyrosine kinase inhibitors in patients with wild-type *EGFR*.

Hong Kong Med J 2018;24(Suppl 4):S34-7
HMRF project number: 11120971

[1] ZY Yang, [1] C Mao, [2] DY Zheng, [1] JL Tang

[1] *Division of Epidemiology, The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong*
[2] *Department of Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong Province, China*

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

Introduction

Lung cancer is the most common cancer and the leading cause of cancer-related mortality in Hong Kong. Approximately 85% of patients with lung cancer have a histological diagnosis of non–small-cell lung cancer (NSCLC). Two thirds of patients with NSCLC are at an advanced stage when diagnosed, and their average survival is 8 to 10 months.

Two specific epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, have been approved for second- or higher-line treatment for advanced NSCLC following failure of prior chemotherapy.[1] Erlotinib has been used as maintenance therapy after four cycles of platinum-based first-line chemotherapy.[2] Both gefitinib and erlotinib are effective as first-line treatment, and gefitinib is effective as maintenance therapy.[3] Nonetheless, among unselected patients with advanced NSCLC, the overall benefit of EGFR-TKIs is limited, possibly because only a subset of recipients responds to the treatment (objective response rate: about 10%). This, together with the risk of adverse events and ensuing costs, prompts us to identify predictors for treatment benefit to help clinical oncologists select patients who are most likely to benefit from EGFR TKIs.

As EGFR TKIs act on the EGFR pathway, molecular alterations along this pathway, such as *EGFR* mutations, high *EGFR* gene copy number, high EGFR protein expression, and *KRAS* mutations, have been indicated as potential predictive biomarkers for treatment by many single-arm studies of patients treated with EGFR TKIs. However, the association between biomarker status and outcome in patients treated with EGFR TKIs may be just a 'prognostic' effect rather than a 'predictive' one. To determine whether a biomarker is predictive of benefits from EGFR TKIs, the efficacy of EGFR TKIs is assessed with stratified (or subgroup) analysis according to biomarker status (eg mutant versus wild-type *EGFR*), which allows testing for the treatment-by-biomarker status interaction.

Previous randomised controlled trials were often statistically underpowered to detect the treatment-by-biomarker status interaction owing to the voluntary nature of tumour tissue donation, insufficient tumour tissues for biomarker testing, or undeterminable testing results. We performed this systematic review and meta-analysis to comprehensively summarise the current best evidence on the predictive values of four biomarkers for EGFR TKIs treatment in patients with advanced NSCLC.

Methods

The MEDLINE, EMBASE, CENTRAL, Chinese Biomedical Database, and Wan Fang Digital Journals databases were searched using the following keywords: 'non-small cell lung cancer', 'tyrosine-kinase inhibitor', 'gefitinib', 'erlotinib', 'biomarker', 'EGFR', and 'KRAS'. The search was limited to human studies, without restriction on the language of publication. Eligible studies were retrieved, and their bibliographies were checked for further relevant publications. If the same patient population was used in several studies, only the largest one or the one

with complete data was used to avoid overlapping. The others were used as supplementary information to obtain relevant data.

Inclusion criteria were: (1) population: patients with locally advanced or metastatic NSCLC; (2) intervention arm: EGFR-TKIs as a monotherapy or in combination with other agents; (3) control arm: chemotherapy, placebo, or no treatment; (4) outcome: progression-free survival, overall survival, and/or objective response; (5) study design: randomised controlled trial; and (6) stratified (or subgroup) analysis by biomarkers: *EGFR* mutations, *EGFR* gene copy number, EGFR protein expression, and/or *KRAS* mutations as detected by analysis of tumour samples.

Data extraction was performed independently by two researchers. Disagreements were resolved by discussion. Unsettled disagreements were settled by a third knowledgeable arbiter whose opinions were final. The data collected included: first author's name, year of publication, study design, number of patients included, number of patients stratified by relevant biomarker status, baseline characteristics of patients in different groups, methods for detection of biomarkers status, previous treatment protocols, study treatment protocols, response criteria, progression-free survival, overall survival, and objective response rate. Clinical outcome variables were extracted according to biomarker and EGFR TKIs treatment status. The quality of included studies was assessed using the Jadad score, a 5-point study quality assessment instrument.[4] The assessment was performed independently by two researchers, with differences resolved by consensus.

The primary outcome was progression-free survival, defined as the period from the start of treatment to disease progression or death from any cause before disease progression. The secondary outcomes included overall survival, defined as the period from the start of treatment to death from any cause; and objective response, defined as the sum of complete and partial responses.

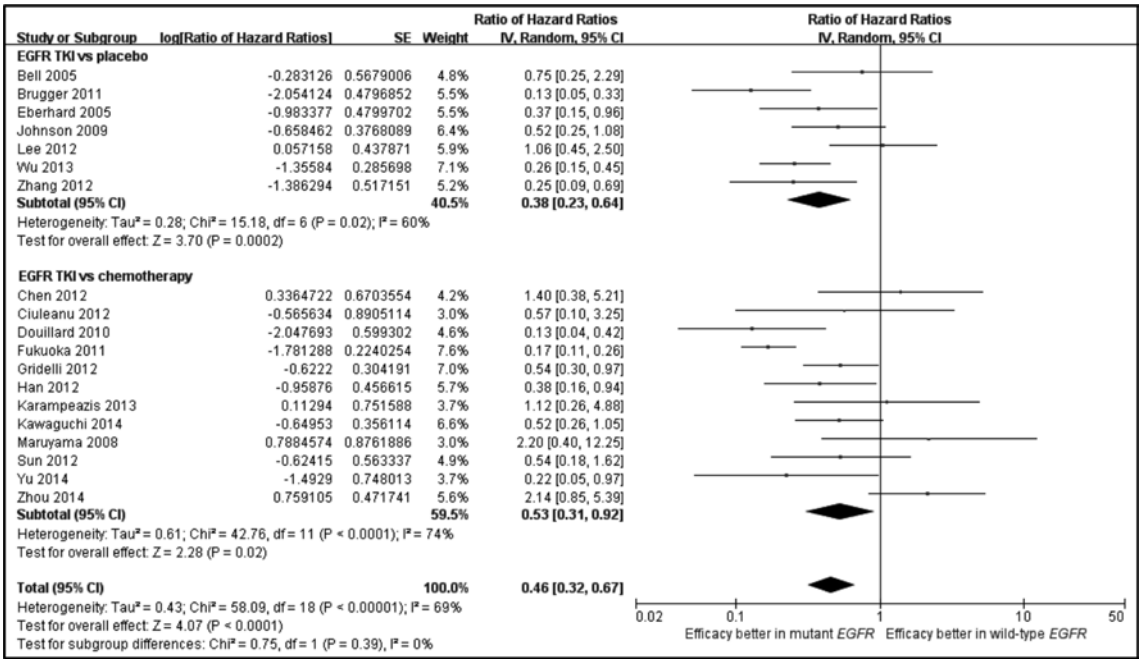
Treatment effects on progression-free survival or overall survival were measured by hazard ratios (HRs) and 95% confidence intervals (CIs). Treatment effects on objective response were expressed as risk ratios (RRs) and 95% CIs. To determine whether a biomarker was predictive of the treatment benefit of EGFR TKIs on an outcome, we calculated the ratio of HRs or RRs and 95% CIs, which indicate the treatment-by-biomarker status interaction, based on the HRs (95% CIs) or RRs (95% CIs) in the biomarker-positive and biomarker-negative subgroups.[5] A ratio of HRs or RRs equal to 1 suggests that the treatment effects of EGFR TKIs are the same in both subgroups. A ratio of HRs <1 means that biomarker-positive patients benefit more from EGFR TKIs than do biomarker-negative patients in terms of progression-free survival or overall survival. Conversely, a ratio of RRs <1 means that biomarker-positive patients benefit less from EGFR TKIs than do biomarker-negative patients in terms of objective response. If appropriate, the ratios of HRs or RRs from different studies were combined for each outcome using a random-effect model. Heterogeneity among studies was assessed by Cochran's *Q*-test and the I^2 statistic. A P value of ≤0.10 for the *Q*-test or an I^2 of >50% is suggestive of substantial between-study heterogeneity. Subgroup analyses according to comparator in trials (placebo or chemotherapy) were conducted to explore sources of heterogeneity. Sensitivity analyses were performed to determine whether study quality affected the final results. Egger's funnel plots were used to assess the possibility of publication bias, as appropriate. All meta-analyses were performed with Review Manager, Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

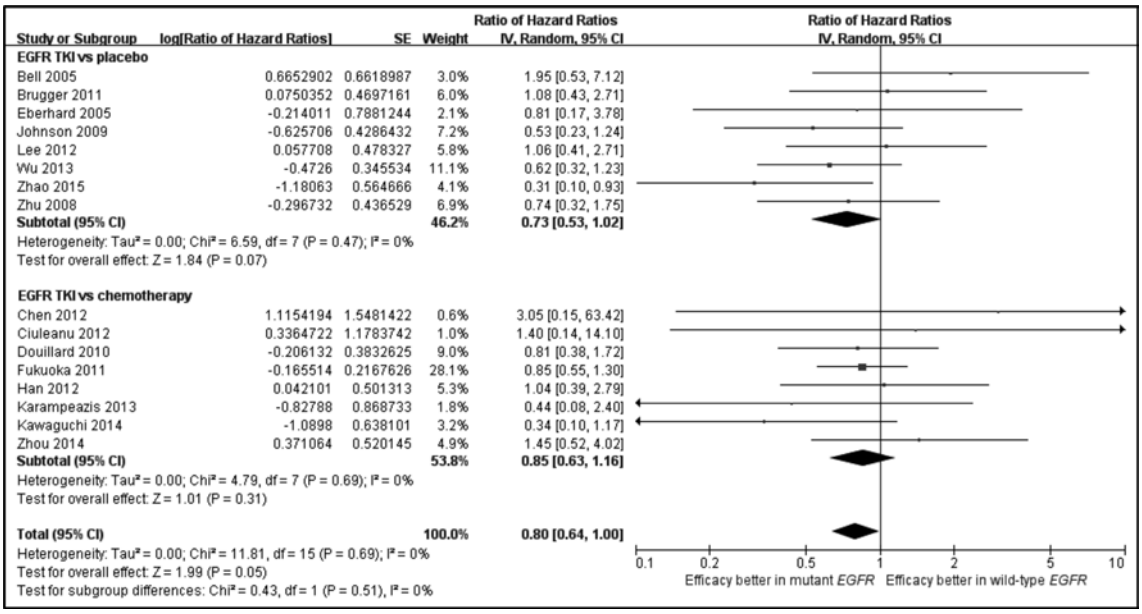
Of the 28 studies included, 21 were on *EGFR* mutations, 12 were on *EGFR* gene copy number, 9 were on EGFR protein expression, and 7 were on *KRAS* mutations. Of the studies, 16 were of high quality, with Jadad scores of 3 to 5, and the rest were of low quality, with Jadad scores of 0 to 2. The number of patients included in analyses of different biomarkers varied from 1872 to 4343. Compared with placebo, EGFR TKIs are effective at increasing progression-free and overall survival, although the effect size is smaller for overall survival than for progression-free survival. EGFR TKIs are comparable to chemotherapy in prolonging both progression-free and overall survival, except among the *EGFR* mutation group, in which EGFR TKIs seem to be much more effective than chemotherapy at prolonging progression-free survival.

For progression-free survival, the summary HRs were 0.46 (95% CI=0.32-0.67, P<0.01, Fig a) for *EGFR* mutations (versus wild-type), 0.72 (95% CI=0.52-0.99, P=0.04) for *EGFR* gene copy number gain (versus no gain), 0.99 (95% CI=0.79-1.24, P=0.92) for EGFR protein expression (versus negative), and 1.40 (95% CI=1.07-1.84, P=0.02) for *KRAS* mutations (versus wild-type). For overall survival, the summary HRs for the four biomarkers were 0.80 (95% CI=0.64-1.00, P=0.05, Fig b), 0.92 (95% CI=0.69-1.23, P=0.57), 0.86 (95% CI=0.70-1.05, P=0.14), and 1.59 (95% CI=1.00-2.54, P=0.05), respectively. For objective response, the summary RRs for the four biomarkers were 3.76 (95% CI=1.91-7.41, P<0.01, Fig c), 0.76 (95% CI=0.32-1.82, P=0.54), 0.40 (95% CI=0.11-1.48, P=0.17), and 0.03 (95% CI=0.00-5.43, P=0.19), respectively. These results indicated that an interaction may exist between EGFR TKIs treatment and *EGFR* mutations (all three

(a)



(b)



(c)

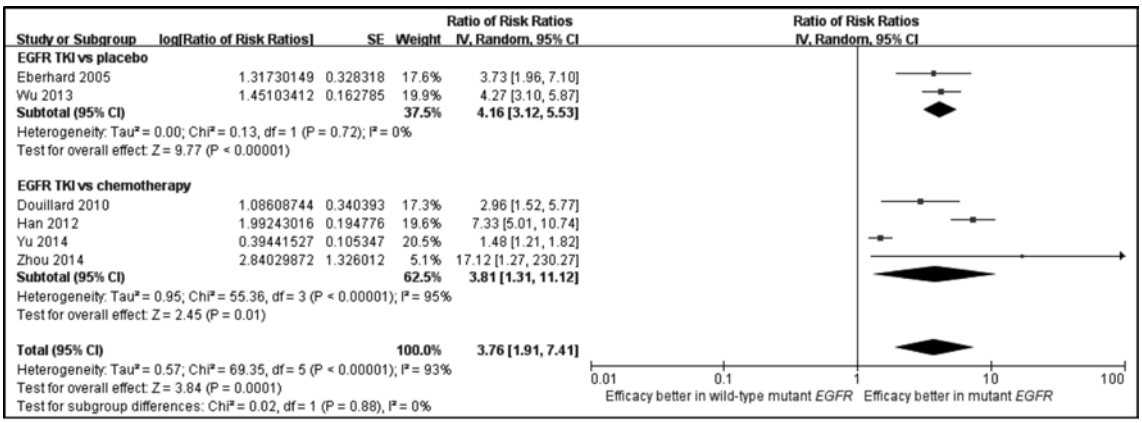


FIG. Interaction between epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) treatment and *EGFR* mutations in terms of (a) progression-free survival, (b) overall survival, and (c) objective response.

outcomes), *EGFR* gene copy number (progression-free survival), and *KRAS* mutations (progression-free survival and overall survival).

Sensitivity analyses conducted by removing studies of low quality did not change the results of the meta-analyses reported above, although the 95% CIs of some interactions tended to be wider owing to the decreased number of studies. Publication bias did not seem to be present.

Discussion

EGFR mutations, *EGFR* gene copy number gain, and *KRAS* mutations are predictive of the treatment effects of EGFR TKIs in advanced NSCLC, with EGFR mutations being the most powerful predictor. However, it is unclear whether the interactions between treatment and *EGFR* gene copy number gain, or between treatment and *KRAS* mutations are independent or mediated by association with *EGFR* mutations. There is no convincing evidence to support the predictive value of EGFR protein expression.

This study has two implications for the decision to use EGFR TKIs to treat advanced NSCLC. First, *EGFR* mutations and possibly *EGFR* gene copy number gain and *KRAS* mutations can help to determine which patients are likely to benefit from EGFR TKIs treatment. Second, chemotherapy is cheaper and causes fewer side effects and thus is generally a better choice, except in patients with *EGFR* mutations in whom EGFR TKIs are a better option. Our findings provide the most comprehensive evidence available for recommendations about current practice guidelines on testing for EGFR mutations.

Acknowledgement

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#11120971).

References

1. Cataldo VD, Gibbons DL, Pérez-Soler R, Quintás-Cardama A. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. N Engl J Med 2011;364:947-55.
2. European Medicines Agency. Information on Tarceva (erlotinib). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000618/human_med_001077.jsp&mid=WC0b01ac058001d124. Accessed 26 July 2015.
3. European Medicines Agency. Information on Iressa (gefitinib). Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001016/human_med_000857.jsp&mid=WC0b01ac058001d124. Accessed 26 July 2015.
4. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1-12.
5. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

Living with advanced breast cancer in women resilient to distress versus women with persistent distress: a qualitative study

WWT Lam*, R Fielding, SW Yoon, J Tsang, I Soong

KEY MESSAGES

1. Cognitive bias in information, thought suppression, social constraints, and pre-existing exposure to life stress were potential risk factors for chronic distress in response to advanced breast cancer.
2. Patients with advanced breast cancer should be assessed for recent exposure to life crises, quality of available family support, and pre-existing emotional problems. Timely referral for relevant supportive services should be implemented.
3. Patient support groups should be introduced to patients in the early phase of breast cancer.
4. Response style and cancer-related rumination should be assessed in women with breast cancer. Early referral to manage maladaptive rumination should be implemented to prevent chronic distress.

Hong Kong Med J 2018;24(Suppl 4):S38-41
HMRF project number: 11121551

[1] WWT Lam, [1] R Fielding, [1] SW Yoon, [3] J Tsang, [3] I Soong

[1] *School of Public Health, The University of Hong Kong*
[2] *Department of Medicine, The University of Hong Kong*
[3] *Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital*

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

Introduction

Improved treatment options have increased survival in women with advanced breast cancer. However, the incurable and progressive nature of the disease makes enormous emotional demands of women living with advanced breast cancer. Yet, most women with locally advanced or metastatic breast cancer have been reported to show little distress; only one in ten have been reported to show persistent distress over time.[1] Understanding the factors that differentiate individuals on distinct distress trajectories is essential to inform therapeutic interventions. Personal attitudes towards and meanings of disease influence how an illness is embodied, lived, and coped with and in turn dictates adjustment to that illness. Hence, construction of illness meaning may play an important role in differentiating women with persistent distress from those with low or transient distress. The present study aimed to compare women with persistent distress and those with low or transient distress in terms of illness meaning of advanced breast cancer and how illness meaning influences their coping strategies. The following questions were addressed: (1) What does being diagnosed with advanced breast cancer mean? That is, how do women fit the diagnosis of advanced breast cancer into their individual life schema? (2) How do the meanings ascribed to advanced breast cancer shape the affected individuals' coping strategies?

Methods

To compare women with persistent distress and those with low or transient distress in response to advanced breast cancer, a sample was drawn from our existing longitudinal study to explore trajectories of psychological distress over the first year following diagnosis of advanced breast cancer. A total of 42 Cantonese- or Mandarin-speaking Chinese women who were diagnosed with locally advanced or metastatic breast cancer and received care from public oncology centres were recruited (Table). Interviews were recorded, transcribed, and analysed following grounded theory approaches using simultaneous analysis.

Results

Narrative analyses identified several distinct characteristics that differentiate women with persistent distress from those with low or transient distress: (1) living through ongoing life crises, (2) information processing bias, (3) thought suppression, and (4) sense of demoralisation. These distinct characteristics were not mutually exclusive but highly interrelated.

For women with persistent distress, the diagnosis of advanced breast cancer was often viewed as another blow in life. A common, distinct feature in women with persistent distress was dealing with ongoing life crises, such as caring for

TABLE. Characteristics of the participants

Case No.	Age, y	Marital status	Occupation	Education	Diagnosis	Distress pattern	Recurrence
1	48	Divorced	Unemployed since diagnosis	Secondary	Non-metastatic	Low	No
2	49	Married	Employed	Secondary	Non-metastatic	Low	No
3	38	Married	Employed	Tertiary	Non-metastatic	Transient	No
4	39	Married	Employed	Tertiary	Non-metastatic	Low	No
5	39	Married	Employed	Tertiary	Non-metastatic	Transient	No
6	53	Married	Unemployed since diagnosis	No education	Non-metastatic	Low	No
7	46	Married	Unemployed since diagnosis	Secondary	Non-metastatic	Transient	No
8	40	Married	Employed	Secondary	Non-metastatic	High	No
9	42	Married	Unemployed since diagnosis	Secondary	Metastatic	Low	Yes
10	59	Married	Employed	Tertiary	Non-metastatic	Low	No
11	47	Married	Homemaker	Secondary	Non-metastatic	Transient	No
12	51	Married	Homemaker	Tertiary	Non-metastatic	Transient	No
13	45	Married	Homemaker	Secondary	Non-metastatic	Low	No
14	45	Divorced	Employed part-time	Tertiary	Non-metastatic	Low	No
15	40	Single	Employed	Secondary	Non-metastatic	Low	No
16	67	Widowed	Retired	Secondary	Metastatic	Low	Yes
17	48	Married	Employed part-time	Tertiary	Non-metastatic	Low	No
18	49	Married	Homemaker	Primary	Metastatic	High	No
19	47	Married	Unemployed	Tertiary	Metastatic	Low	No
20	44	Married	Unemployed	Primary	Non-metastatic	High	No
21	50	Single	Employed	Secondary	Metastatic	Transient	No
22	67	Married	Unemployed since diagnosis	Primary	Metastatic	Low	Yes
23	73	Married	Homemaker	Primary	Metastatic	Low	Yes
24	53	Married	Unemployed since diagnosis	Primary	Metastatic	High	Yes
25	58	Married	Retired	Secondary	Metastatic	High	No
26	35	Married	Employed	Tertiary	Non-metastatic	Low	No
27	30	Single	Employed	Tertiary	Non-metastatic	Transient	No
28	52	Single	Unemployed before diagnosis	Secondary	Non-metastatic	Low	No
29	40	Single	Employed	Secondary	Non-metastatic	Transient	No
30	60	Married	Homemaker	Primary	Metastatic	Low	Yes
31	48	Single	Employed	Secondary	Metastatic	Low	No
32	57	Married	Employed	Secondary	Non-metastatic	High	No
33	47	Married	Homemaker	Secondary	Metastatic	Transient	No
34	58	Widowed	Employed	Primary	Metastatic	Transient	Yes
35	46	Married	Employed	Secondary	Non-metastatic	Transient	No
36		Married	Homemaker	Secondary	Metastatic	Transient	Yes
37	53	Married (husband died during the study)	Unemployed after diagnosis	Secondary	Non-metastatic	High	No
38	53	Married	Unemployed after diagnosis	Primary	Metastatic	High	No
39	43	Widowed	Unemployed after diagnosis	Secondary	Non-metastatic	High	No
40	47	Married	Unemployed after diagnosis	Secondary	Non-metastatic	High	No
41	47	Married	Unemployed since diagnosis	Tertiary	Metastatic	Transient	Yes
42	46	Divorced	Homemaker	Primary	Non-metastatic	High	No

family members with chronic or terminal illness, loss of spouse, marriage failure, or work stress.

> *"I was very upset (about the diagnosis). I asked myself, 'Why is this happening to us'? My husband was diagnosed with lung cancer. Now it's me.... His condition has been stable for a while. After I got sick, his condition got worse. When I was having chemotherapy, his condition deteriorated rapidly and he was hospitalised. I had to look after him when I was having chemo. He was very picky. Apart from me, he wouldn't let anyone else feed him.... At one time, I said to my husband, 'Perhaps we should just end our life together'. It was just a thought, of course. We had to keep it going.... After I finished the radiation therapy, my husband passed away. It was very, very hard..." (case 37)*

Owing to their chronic ongoing life stress, these women often had pre-existing emotional problems. Some had previously sought help from psychiatrists or clinical psychologists but were in remission before the cancer diagnosis. The cancer diagnosis triggered relapse of the emotional instability.

> *"My former job was very stressful.... I was also very anxious. I always thought, 'why is my life so bad'? It's so unfair. I was referred to a psychiatrist. The doctor gave me some medication." (case 39)*

Another characteristic of women with persistent distress was attentional and interpretational bias toward threat-related information. Although most women reported physical symptom distress, women with persistent distress expressed difficulties shifting their thoughts away from the unmanaged physical symptoms. They often exhibited vigilant behaviour and intrusive cancer-related thoughts. Furthermore, they often interpreted these as signs of cancer recurrence or disease progression.

> *"I got very worried when I wasn't well about things like having pain. I couldn't help but keep thinking about it. It was very stressful. I felt helpless." (case 43)*

To deal with their intrusive thoughts, some patients attempted to suppress their thoughts by forcing themselves not to think about their illness and avoiding situations that reminded them about their illness.

> *"I don't want to talk about this (my illness). My life is a tragedy. I force myself not to think about it. Whenever I talk about it, I cry.... I don't join the activities organised by the cancer resource centre. I don't like to meet other patients with cancer. I don't want to be reminded about (my illness)." (case 42)*

Many patients with persistent distress exhibited demoralisation syndrome, including senses of hopelessness and helplessness, feelings of being trapped, and lack of motivation to cope effectively.

> *"I feel hopeless. There is no cure. There is no hope.... Just waiting. When it's time, that is it." (case 38)*

In contrast to women with persistent distress, women with transient distress adopted various strategies to cope with the demands of the illness, including acceptance, taking charge, and social support. Rumination on cancer and its impacts was perceived as ineffective for coping with the demands. Some patients refused to let the illness take over their lives. Instead, they proactively maintained their normal routines. In contrast to women with persistent distress who avoided social support from peers, women with transient distress viewed patient support groups as effective coping resources. Mutual sharing with other patients with advanced breast cancer helped these women come to terms with the diagnosis.

> *"I was very down when I found out that I need chemo. But it's only temporary. I didn't let myself think about it. I just focused on completing the treatment and getting on with my life."*
>
> *"I had to look after myself. I had to take charge. If I want to be healthy, I need to treat myself well." (taking charge: case 35) (acceptance: case 27)*

> *"I met so many patients like me. It made me realise that the disease is not as horrible as I thought. Now I know that having this illness doesn't equate to a death sentence." (social support: case 36)*

Women with low, stable distress shared common features with respect to coping with illness demands with those of women with transient distress. However, several additional features seem to be linked to their resilience, including living in the present and having a pre-existing stable, supportive family.

> *"I am not upset or scared. I don't worry. I try to live fully each day." (living in the present: case 04)*

> *"I am lucky that I have a supportive husband. I don't have to worry about my family." (supportive family: case 22)*

Discussion

The narratives of women with persistent distress highlighted how the illness permeates every aspect of their lives and often leads to a sense of demoralisation.[2] In contrast, women with low, stable or transient distress were able to encapsulate the illness with minimum impacts on their lives.[2] Cognitive biases in information processing were a key differentiating factor in women's illness representations. Women with persistent distress

were not only vigilant towards somatic and cancer-related threats but also had difficulties with disengaging from these threats. To cope with the perseverative negative thinking, cognitive avoidance was commonly used by women with persistent distress. These women acknowledged their inability to control their own worry and rumination, which prompted them to attain control over their negative thinking using thought suppression. This was counterproductive and resulted in increased levels of intrusive thoughts and attentional bias towards somatic and cancer-related information.

In contrast, women with low, stable or transient distress did not engage in dysfunctional repetitive thoughts. They were able to accept and/or live in the present moment, a component of mindfulness practice.[3] Mindfulness may reduce anxiety and depression symptoms among patients with cancer.[3] Hence, mindfulness-based intervention may be beneficial to women with persistent distress who have attentional bias toward cancer-related threats.

The role of social support (family and peer support groups) was also highlighted in the narrative analysis. Women with low, stable or transient distress received encouragement from their peers and families to adopt positive coping strategies. In contrast, women with persistent distress were often in unsupportive environments that likely promoted thought and emotion suppression.

Exposure to multiple life stresses was another differentiating factor. Previous or current life stress has commonly been reported in women with persistent distress, and they have been reported to be more vulnerable in terms of coping with cancer impacts.[4] Similarly, people who are depressed show selective recall of negative events.[5]

Conclusions

Cognitive processing, social resources, and exposure to life stress influence how women cope with advanced breast cancer. Cognitive bias in terms of information, thought suppression, social constraints, and pre-existing exposure to life stress were the potential risk factors for chronic distress in response to advanced breast cancer.

Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#11121551). We thank all of the participants and research assistants for their contributions.

References

1. Lam WW, Soong I, Yau TK, et al. The evolution of psychological distress trajectories in women diagnosed with advanced breast cancer: a longitudinal study. Psychooncology 2013;22:2831-9.
2. Nerenz DR, Leventhal H. Self-regulation theory in chronic illness. In: Coping with Chronic Disease: Research and Applications. Burish TG, Bradley LA, eds. New York, NY: Academic Press; 1983: 12-37.
3. Piet J, Wurtzen H, Zachariae R. The effect of mindfulness-based therapy on symptoms of anxiety and depression in adult cancer patients and survivors: a systematic review and meta-analysis. J Consult Clin Psychol 2012;80:1007-20.
4. Bonanno GA, Westphal M, Mancini AD. Resilience to loss and potential trauma. Annu Rev Clin Psychol 2011;7:511-35.
5. Mathews A, MacLeod C. Cognitive vulnerability to emotional disorders. Annu Rev Clin Psychol 2005;1:167-95.

Cross-cultural adaptation of the Tinnitus Functional Index for measurement of chronic tinnitus in Hong Kong Chinese patients

ACS Kam*, EKS Leung, PYB Chan, APP Cheung, MCF Tong

KEY MESSAGES

1. The 25-item Chinese version of the Tinnitus Functional Index (TFI-CH) is a valid, reliable, and responsive tool to measure tinnitus severity and related negative impacts.
2. The TFI-CH has comprehensive coverage of tinnitus severity, as the same eight factors (intrusive, sense of control, cognitive, sleep, auditory, relaxation, quality of life, and emotion) from the original TFI were extracted.

Hong Kong Med J 2018;24(Suppl 4):S42-5
HMRF project number: 11120221

[1] ACS Kam, [2] EKS Leung, [3] PYB Chan, [4] APP Cheung, [5] MCF Tong

[1] *Department of Special Education and Counselling, The Education University of Hong Kong*
[2] *Department of ENT, Prince of Wales Hospital*
[3] *Department of ENT, Pamela Youde Nethersole Eastern Hospital*
[4] *Department of ENT, Yan Chai Hospital*
[5] *Department of Otorhinolaryngology, Head and Neck Surgery, The Chinese University of Hong Kong*

* Principal applicant and corresponding author: annakam@eduhk.hk

Introduction

Tinnitus is a self-reported phenomenon that is not readily apparent to others. Subjective psychometric measures are used to assess the severity and impacts of tinnitus and to determine the effectiveness of intervention. The Tinnitus Functional Index (TFI) was developed by a group of audiologists, otologists, hearing scientists, and other health researchers.[1,2] It is a 25-item self-administered questionnaire that assesses eight domains of negative tinnitus impact (intrusive, sense of control, cognitive, sleep, auditory, relaxation, quality of life, and emotion) using an 11-point scale (0-10). The overall score ranges from 0 to 100; higher scores indicate greater severity. The TFI has good test-retest reliability, convergent validity, and discriminant validity.[2] Effect size has been measured as moderate to large (0.74-1.01) at 3 months and larger (1.19-1.88) at 6 months after the first treatment session. The TFI is valid for assessment of the severity and negative impacts of tinnitus at initial assessment and treatment-related changes (responsiveness) and covers multiple domains of tinnitus severity.[2]

This study aimed to translate the TFI into Chinese and to validate its use in Hong Kong Chinese patients with chronic tinnitus. Its psychometric properties (reliability, construct validity, and responsiveness) were determined.

Methods

The original TFI was translated into Chinese using the translation-back-translation method.[3] The corresponding author of the original TFI helped us to assess the equivalence of the back-translation to the original. A pilot test on 30 subjects was conducted before finalisation.

A total of 124 consecutive adult tinnitus patients were recruited from the Prince of Wales Hospital, Pamela Youde Nethersole Eastern Hospital, and Yan Chai Hospital. Informed consent was obtained from each patient before the first tinnitus consultation. Patients were interviewed, and their demographics, symptoms, and comorbidities were recorded. Patients were asked to complete the Chinese version of the Tinnitus Functional Index (TFI-CH), the Chinese version of the Tinnitus Handicap Inventory (THI-CH), and the Chinese version of the Short-Form 36 Health Survey (SF-36).[4] Patients were asked to rate tinnitus severity on a visual analogue scale (VAS) of 0 to 100 in terms of tinnitus loudness, annoyance, acceptance, emotional disturbance, sleep disturbance, ability to concentrate, stress, worry, ease of communication, life satisfaction, and tinnitus severity.

Twenty-five of the patients were selected at random for retest of the TFI-CH, THI-CH, VAS for tinnitus severity and questionnaires about history of treatments received and global perception of change. For global perception of change, patients were asked to rate the overall change in tinnitus condition between the present situation and the first visit to the tinnitus clinic on a 7-point scale from 1 (much improved) to 7 (much worse).[2]

Follow-up data were collected at 3 months and 6 months after the first tinnitus treatment session using pre-stamped mail.

Internal consistency reliability was assessed

using Cronbach's alpha coefficients and item-total correlation analyses. Test-retest reliability was assessed using the intraclass correlation coefficient. Confirmatory factor analysis was performed to check whether the eight factors could still be identified in the TFI-CH. Convergent and discriminant validity were assessed with correlational analyses on initial TFI-CH and THI-CH scores, VAS for tinnitus severity, and the Chinese version of the SF-36. The effect size for the TFI-CH was compared with that for the THI-CH and the VAS for tinnitus severity after 3 months and 6 months.

Results

A total of 71 women and 53 men completed assessment at baseline; 93 and 58 of the patients completed the 3-month and 6-month follow-ups, respectively. The patients were aged 23 to 83 (mean, 53.98; standard deviation, 10.55) years. The mean time since onset of tinnitus was 5.61 (standard deviation, 7.58) years. Tinnitus noise was continuous in 76.6% of patients and was unilateral in 47.6% of patients.

The internal consistency of the TFI-CH was assessed using Cronbach's alpha coefficients and item-total correlations. The Cronbach's alpha for the total scale was 0.97, indicating a high degree of internal consistency. The item-total correlations ranged from 0.45 (item 4: "Over the past week, did you feel in control in regard to your tinnitus?") to 0.85 (item 16: "Over the past week, how much has your tinnitus interfered with your quiet resting activities?"). The test-retest correlation (intraclass correlation coefficient) was 0.84 (P<0.01), indicating good test-retest reliability.

A confirmatory factor analysis was conducted on all subjects (n=124). In the original TFI, items 1 to 3 loaded onto the intrusive factor; items 4 to 6, the sense of control factor; items 7 to 9, the cognitive factor; items 10 to 12, the sleep factor; items 13 to 15, the auditory factor; items 16 to 18, the relaxation factor; items 19 to 22, the quality of life factor; and items 23 to 25, the emotional factor. A Chi squared test of model fit for the confirmatory factor analysis with an eight-factor solution rejected the null hypothesis that the designated free and fixed factor loadings hold, $\chi^2(247\ df)=419.32$ (P<0.001). The comparative fit index was 0.95 and the Tucker-Lewis index was 0.93. The root mean square error of approximation for this model indicated mediocre fit (0.075, 90% confidence interval=0.063-0.087). The standardised root mean residual was 0.045 (P<0.05). Thus, this eight-factor model was a good fit. The standardised factor loadings from the confirmatory factor analysis are shown in Table 1.

The construct validity of the TFI-CH was evaluated using correlations with the THI-CH, the VAS for tinnitus severity, and SF-36. Pearson's product-moment correlation analysis was performed. The overall TFI-CH score was strongly correlated with the THI-CH total score (r=0.86, P<0.01), moderately correlated with the VAS for tinnitus severity (r=0.68, P< 0.01) [Table 2], and weakly to moderately correlated with the SF-36 subscale scores (r=0.28-0.62, P<0.01).

The effect sizes of the TFI-CH overall scale and subscales were examined in terms of criterion

TABLE 1. Standardised factor loadings for the confirmatory factor analysis

Factor	Estimate	Standard error	Estimate / standard error	P value (two-tailed)
Intrusive				
I3: Recoded % annoyed	0.87	0.03	25.49	<0.001
I1: Recoded % aware	0.59	0.07	9.03	<0.001
I2: Strong or loud	0.67	0.06	11.94	<0.001
Sense of control				
SC6: Easy to ignore	0.78	0.05	16.07	<0.001
SC4: Feel in control	0.56	0.07	7.81	<0.001
SC5: Easy to cope	0.69	0.06	11.52	<0.001
Cognitive				
C7: Concentrate	0.91	0.02	42.76	<0.001
C8: Think clearly	0.86	0.03	32.24	<0.001
C9: Focus attention	0.87	0.03	32.80	<0.001
Sleep				
SL11: As much sleep	0.96	0.02	60.02	<0.001
SL10: Difficult to fall asleep, stay asleep	0.91	0.02	45.47	<0.001
SL12: Keep from sleeping deeply, peacefully	0.83	0.03	26.97	<0.001
Auditory				
A15: Follow conversations	0.91	0.02	41.43	<0.001
A14: Understand people	0.91	0.02	43.67	<0.001
A13: Hear clearly	0.87	0.03	31.86	<0.001
Relaxation				
R16: Quiet resting activities	0.93	0.02	63.35	<0.001
R17: Ability to relax	0.95	0.01	77.98	<0.001
R18: Enjoy peace and quiet	0.91	0.02	48.74	<0.001
Quality of life				
Q20: Enjoyment of life	0.92	0.02	51.22	<0.001
Q19: Enjoy social activities	0.91	0.02	49.32	<0.001
Q21: Relationships family and friends	0.91	0.02	48.63	<0.001
Q22: Difficulty performing work or tasks	0.84	0.03	29.45	<0.001
Emotional				
E24: Bothered or upset	0.95	0.02	64.90	<0.001
E23: Anxious or worried	0.92	0.02	52.55	<0.001
E25: Depressed	0.82	0.03	24.69	<0.001

TABLE 2. Pearson's correlations among different scales

Scale	Total	Chinese version of the Tinnitus Functional Index subscale							
		Intrusive	Sense of Control	Cognitive	Sleep	Auditory	Relaxation	Quality of Life	Emotional
Chinese version of the Tinnitus Handicap Inventory									
Total	0.86†	0.62†	0.56†	0.75†	0.61†	0.69†	0.76†	0.84†	0.84†
Emotional	0.78†	0.57†	0.48†	0.67†	0.53†	0.61†	0.72†	0.78†	0.83†
Functional	0.84†	0.60†	0.50†	0.75†	0.59†	0.74†	0.74†	0.85†	0.78†
Catastrophic	0.67†	0.51†	0.61†	0.57†	0.53†	0.42†	0.54†	0.57†	0.64†
Visual analogue scale for tinnitus severity									
Tinnitus loudness	0.67†	0.73†	0.48†	0.62†	0.51†	0.56†	0.56†	0.58†	0.51†
Tinnitus annoyance	0.75†	0.64†	0.55†	0.57†	0.64†	0.51†	0.68†	0.60†	0.73†
Tinnitus acceptance	–0.52†	–0.19*	–0.38†	–0.42†	–0.51†	–0.33†	–0.48†	–0.43†	–0.57†
Emotional disturbance	–0.56†	–0.39†	–0.39†	–0.53†	–0.38†	–0.45†	–0.48†	–0.53†	–0.62†
Sleep disturbance	–0.55†	–0.32†	–0.40†	–0.42†	–0.62†	–0.36†	–0.46†	–0.44†	–0.51†
Concentration	–0.59†	–0.43†	–0.38†	–0.62†	–0.35†	–0.45†	–0.55†	–0.61†	–0.54†
Stress	0.65†	0.46†	0.33†	0.61†	0.41†	0.54†	0.62†	0.65†	0.68†
Worries	0.69†	0.51†	0.45†	0.60†	0.48†	0.53†	0.65†	0.62†	0.70†
Communication difficulty	–0.51†	–0.36†	–0.35†	–0.55†	–0.17	–0.59†	–0.40†	–0.61†	–0.42†
Life satisfaction	–0.58†	–0.40†	–0.44†	–0.60†	–0.28†	–0.57†	–0.48†	–0.58†	–0.54†
Severity	0.68†	0.68†	0.48†	0.56†	0.59†	0.54†	0.54†	0.54†	0.58†
Short Form 36 Health Survey									
Physical function	–0.28†	–0.15	–0.10	–0.28†	–0.20*	–0.29†	–0.25†	–0.36†	–0.25†
Role physical	–0.53†	–0.30†	–0.31†	–0.47†	–0.44†	–0.43†	–0.45†	–0.51†	–0.46†
Body pain	–0.37†	–0.22*	–0.21*	–0.35†	–0.26†	–0.31†	–0.33†	–0.41†	–0.39†
General health	–0.34†	–0.26†	–0.32†	–0.34†	–0.24†	–0.16	–0.25†	–0.33†	–0.37†
Vitality	–0.44†	–0.28†	–0.27†	–0.46†	–0.26†	–0.34†	–0.34†	–0.46†	–0.43†
Social functioning	–0.48†	–0.32†	–0.31†	–0.42†	–0.30†	–0.34†	–0.40†	–0.51†	–0.41†
Role emotional	–0.52†	–0.34†	–0.27†	–0.52†	–0.30†	–0.41†	–0.51†	–0.53†	–0.45†
Mental health	–0.62†	–0.42†	–0.30†	–0.59†	–0.40†	–0.44†	–0.62†	–0.64†	–0.66†

* P<0.05 (2-tailed)
† P<0.01 (2-tailed)

groups of improved, unchanged, and worse based on the global perception of change at 3 and 6 months (Table 3). Effect sizes were calculated using Cohen's *d* and ranged from small to large. Positive and negative effect sizes were obtained in the improved and worse groups, respectively. Effect sizes for the unchanged groups were closest to zero. Overall, the effect sizes of the improved and worse groups were larger for the TFI-CH than for the THI-CH or the VAS for tinnitus severity at 3 and 6 months.

Discussion

The TFI-CH has good internal consistency, with a Cronbach's alpha of 0.97, which is the same as that of the original TFI. Test-retest reliability was good, with an intraclass correlation coefficient of 0.84. Factor analysis showed comparable results with the original TFI. The same eight factors were extracted with the same item compositions of subscales in the TFI and TFI-CH.

Convergent validity with the TFI-CH was high (r=0.86, P<0.01), and that with the VAS for tinnitus severity was moderate (r=0.68, P<0.01). TFI-CH scores were also moderately correlated with the SF-36 subscales of mental health (r=0.62, P<0.01), role physical (r=0.53, P<0.01), and role emotional (r=0.52, P<0.01), but these correlations were weaker than that of the VAS for tinnitus severity. This indicates that tinnitus-related complaints

TABLE 3. Effect size estimates for the overall scales and subscales at 3 and 6 months

Scale	Perceived change in overall tinnitus condition					
	At 3 months			At 6 months		
	Improved (n=19)	Unchanged (n=43)	Worse (n=31)	Improved (n=11)	Unchanged (n=46)	Worse (n=15)
Chinese version of the Tinnitus Functional Index	0.50	–0.27	–1.08	0.38	–0.29	–0.86
Chinese version of the Tinnitus Handicap Inventory	0.13	–0.34	–0.87	1.15	–0.37	–0.53
Visual analogue scale for tinnitus severity	0.33	–0.19	0.14	–0.40	0.08	0.23
Chinese version of the Tinnitus Functional Index subscales						
Intrusive	0.23	–0.14	–0.32	0.31	–0.14	–0.45
Sense of control	0.58	–0.38	0.20	0.18	–0.19	–0.55
Cognitive	1.22	–0.69	0.53	0.09	–0.51	–1.25
Sleep	0.75	–0.35	0.40	0.42	–0.25	–0.51
Auditory	0.72	–0.41	0.57	0.29	–0.36	–0.69
Relaxation	1.03	–0.73	0.03	–0.23	–0.53	–0.89
Quality of life	0.91	–0.46	0.18	0.41	–0.42	–1.27
Emotional	1.29	–0.47	0.90	0.22	–0.25	–0.70
Chinese version of the Tinnitus Handicap Inventory subscales						
Functional	0.19	–0.32	–0.70	1.00	–0.06	1.03
Emotional	0.11	–0.32	–0.82	0.92	–0.09	1.17
Catastrophic	0.00	–0.39	–0.71	0.93	–0.07	1.30

are different from general psychopathological symptoms and syndromes.[5] Divergent validity was demonstrated.

The TFI-CH had good responsiveness, with stronger effect sizes for detecting change (treatment effects) than the THI-CH at 3 months. A similar trend was observed at 6 months, except among the improved group. Caution should be taken in interpreting the results because of the small sample size. The effect sizes for some TFI-CH subscales were small, and use of the overall scale score is recommended.

Limitations

Only three criterion groups were included in the effect size estimation. It is unknown whether the TFI-CH is sensitive to more subtle changes in tinnitus condition. The present study did not control for the type of tinnitus treatment patients received. Differences between various treatments may have led to increased variance in treatment-related changes and restriction of the range of effect sizes.[2]

Conclusion

The TFI-CH is a valid, reliable, and responsive tool to measure tinnitus severity and related negative impacts in Chinese patients.

Acknowledgement

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#11120221).

References

1. Wilson PH, Henry JL. Psychological management of tinnitus. In: Tyler R, editor. Tinnitus Handbook. San Diego: Singular Publishing Group; 2000: 263-80.
2. Meikle MB, Henry JA, Griest SE, et al. The tinnitus functional index: development of a new clinical measure for chronic, intrusive tinnitus. Ear Hear 2012;33:153-76.
3. Bradley C. Translation of questionnaires for use in different languages and cultures. In: Bradley C, editor. Handbook of Psychology and Diabetes. Churchill: Harwood; 1994: 43-55.
4. Lam CL, Gandek B, Ren XS, Chan MS. Tests of scaling assumption and construct validity of the Chinese (HK) version of the SF-36 Health Survey. J Clin Epidemiol 1998;51:1139-47.
5. Hiller W, Goebel G, Rief W. Reliability of self-rated tinnitus distress and association with psychological symptom patterns. Br J Clin Psychol 1994;33:231-9.

Effect of short-term high-intensity noise exposure on auditory physiology: a functional magnetic resonance imaging study

C Lau*

KEY MESSAGES

1. Short-duration, high-intensity noise exposure changes midbrain auditory processing.
2. Functional magnetic resonance imaging is sensitive to such changes, which are temporary and reversible in weeks and are likely related to more permanent changes in the inner ear and auditory nerve.

Hong Kong Med J 2018;24(Suppl 4):S46-7
HMRF project number: 11122581

C Lau

Department of Physics, City University of Hong Kong

* Principal applicant and corresponding author: condon.lau@cityu.edu.hk

Introduction

The present study investigated changes in the central auditory system following short-duration, high-intensity noise exposure. Normal female Sprague-Dawley rats were exposed to 100-dB sound pressure level noise for 15 minutes. The auditory system of each rat was scanned using functional magnetic resonance imaging (fMRI) to determine the blood-oxygen-level-dependent signal at three timepoints (before exposure and at days 7 and 14 after the exposure). fMRI was sensitive to the resulting functional changes to the central auditory system.

Results

Figure 1 shows the t-value maps at three timepoints (days 0, 7, and 14) with 12- and 20-kHz stimulation. For 12-kHz stimulation, t-values were highest at days 0 and 14 and lowest at day 7 in the inferior colliculus, whereas t-values were highest at day 0, slightly lower at day 14, and lowest at day 7 in the lateral lemniscus. For 20-kHz stimulation, t-values were highest at day 0 and lower at days 7 and 14 in the inferior colliculus and highest at day 0, slightly lower at day 14, and lowest at day 7 in the lateral lemniscus. Thus, there were transient changes in fMRI responses following short-duration, high-intensity noise exposure.

Tukey's honest significant difference test showed that signal amplitudes in the inferior colliculus were significantly greater at day 0 than day 7 for 12-kHz stimulation ($P<0.01$) and 20-kHz simulation ($P<0.001$), and they were also significantly greater at day 14 than day 7 for 12-kHz and 20-kHz simulation ($P<0.05$). Overall, fMRI responses were significantly reduced at day 7 and largely recovered at day 14.

Figure 2 shows the blood-oxygen-level-dependent signal amplitudes measured from the inferior colliculus at the three time-points. The orders of signal amplitudes from highest to lowest were those at days 0, 14, and 7 for 12-kHz stimulation ($P<0.05$), and those at days 0, 14, and 7 for 20-kHz stimulation ($P<0.01$). Noise exposure significantly reduced fMRI response in the inferior colliculus at day 7, but the response had largely recovered at day 14.

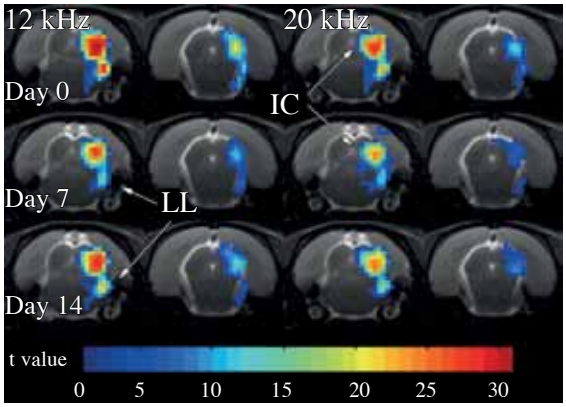


FIG 1. Functional magnetic resonance imaging showing the mean t-value maps immediately after 15 minutes of exposure to 100-dB sound pressure level noise (day 0), 7 days after exposure (day 7), and 14 days after exposure (day 14). Activation maps acquired with 12-kHz and 20-kHz noise stimulation are overlaid on anatomical images. Activation is mainly observed in the inferior colliculus (IC) and lateral lemniscus (LL) in the hemisphere contralateral to the stimulated left ear.

Discussion

Short-duration, high-intensity noise exposure results in transient reduction in fMRI responses in the auditory midbrain of rats. The reductions

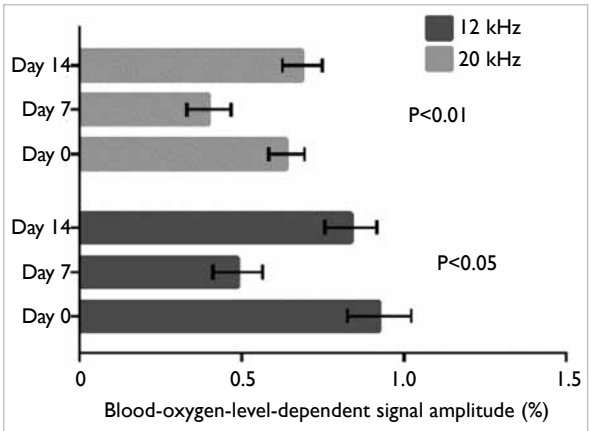


FIG 2. Blood-oxygen-level-dependent signal amplitude (%) in the inferior colliculus (n=10) before exposure and 7 and 14 days after exposure to 12-kHz and 20-kHz stimulation. The signal amplitude is significantly reduced at day 7 after exposure and largely recovers at day 14.

were observed 7 days after noise exposure. These reductions occurred even in the absence of auditory brainstem response threshold elevations, suggesting that the changes were of central origin. The midbrain responses had largely recovered to pre-exposure levels at day 14.

Exposure to high sound pressure level can cause permanent hearing loss and tinnitus. Hearing loss involves an increase in the minimum detectible sound pressure level threshold. Occupational health standards have documented exposure limits. Exposures that do not permanently shift thresholds may still contribute to difficulty comprehending speech and hyperacusis. Noisy environments contribute to sleep loss, cardiovascular disease, and stress. Noise exposure (or the absence thereof) also affects auditory physiology. For example, cochlear implantation alters auditory cortical function.[1,2] Hearing loss at certain frequencies causes neurons normally sensitive to those frequencies to adjust to neighbouring frequencies.[3-5] The results of this study provide insight on how central auditory processing is affected by exposure to high sound pressure level.

Exposure to high sound pressure level also leads to long-term loss of afferent nerve terminals on inner hair cells and degeneration of the cochlear nerve.[6] In mice exposed to 100-dB sound pressure level noise for 2 hours, their auditory brainstem response and compound action potential thresholds returned to pre-exposure levels 2 weeks later.[6] However, suprathreshold responses decreased at high frequencies. There was no loss of hair cells, but there was degeneration of presynaptic and postsynaptic elements around inner hair cells in the high-frequency portion of the cochlea within 24 hours. At 1-year post-exposure, there was significant reduction in the spiral ganglion cell count in the high-frequency region. This reduction was not significant at 2 weeks post-exposure.

Conclusions

Central structures of the auditory system, such as the lateral lemniscus and inferior colliculus, and possibly even higher auditory structures, are related to degeneration of the cochlea and surrounding structures. This relationship is observed 1 to 2 weeks following noise exposure. fMRI can detect transient changes in inferior collicular responses long before significant spiral ganglion cell reduction in the cochlea has set in. The fMRI signal reduction may be related to decreased auditory brainstem suprathreshold responses.[6] Suprathreshold decreases primarily occur at much higher frequencies (32 kHz) and are permanent. Therefore, the recovery observed may indicate the central auditory system's ability to compensate for the peripheral damage.

Acknowledgements

This study was supported by the Health and Medical Research Fund, Food and Health Bureau, Hong Kong SAR Government (#11122581), the Hong Kong General Research Fund (#661313), and start-up funding from the City University of Hong Kong and the Hong Kong University of Science and Technology.

References

1. Pantev C, Dinnesen A, Ross B, Wollbrink A, Knief A. Dynamics of auditory plasticity after cochlear implantation: a longitudinal study. Cereb Cortex 2006;16:31-6.
2. Seghier ML, Boex C, Lazeyras F, Sigrist A, Pelizzone M. FMRI evidence for activation of multiple cortical regions in the primary auditory cortex of deaf subjects users of multichannel cochlear implants. Cereb Cortex 2005;15:40-8.
3. Izquierdo MA, Gutierrez-Conde PM, Merchan MA, Malmierca MS. Non-plastic reorganization of frequency coding in the inferior colliculus of the rat following noise-induced hearing loss. Neuroscience 2008;154:355-69.
4. Kamke MR, Brown M, Irvine DR. Plasticity in the tonotopic organization of the medial geniculate body in adult cats following restricted unilateral cochlear lesions. J Comp Neurol 2003;459:355-67.
5. Robertson D, Irvine DR. Plasticity of frequency organization in auditory-cortex of guinea pigs with partial unilateral deafness. J Comp Neurol 1989;282:456-71.
6. Kujawa SG, Liberman MC. Adding insult to injury: cochlear nerve degeneration after "temporary" noise-induced hearing loss. J Neurosci 2009;29:14077-85.

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.