SUPPLEMENT 2

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# Health and Medical Research Fund

## Research Dissemination Reports

# 醫療衞生研究基金

## 研究成果報告

Cancer
癌症

Health services research
醫療服務研究

Modifiable risk factors
可改變風險因素

Chinese Medicine
中醫藥

Mental health
精神健康

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# Editorial

Dissemination reports are concise informative reports of health-related research supported by the Health and Medical Research Fund administered by the Health Bureau. In this edition, we present 12 dissemination reports of projects related to cancer, health services research, modifiable risk factors, Chinese medicine, and mental health. In particular, research findings of three projects may provide insights to enhance clinical practices and help inform health policy formulation in Hong Kong.

Circulating tumour cells (CTCs) are shed from primary or metastatic tumours into the bloodstream and can act as seeds for metastasis. They are present in minute quantities among other blood cell types. New analytical techniques allow CTCs to be identified and used as predictive biomarkers for monitoring tumour molecular heterogeneity and evolving drug resistance. Lung[1] used longitudinal serial real-time monitoring of CTCs and cell-free DNA in blood from 57 patients with advanced oesophageal squamous cell carcinoma to provide supplementary prognostic information for risk stratification. Further development of this non-invasive technique may be useful clinically for prospective serial longitudinal monitoring to support decision in clinical management.

Geriatric hip fractures are common among older adults in Hong Kong. In 2007, the Hospital Authority adopted a clinical pathway for management of geriatric hip fractures. The length of hospital stay was reduced by 6.1 days in acute hospitals with concomitant reduction in average manpower cost. Since late 2018, a new orthogeriatric co-management model involving geriatricians in acute and rehabilitation phases has been implemented to further improve the outcome and cost-effectiveness. Leung et al[2] evaluated the new model using data from 401 eligible patients receiving either conventional orthopaedic care or orthogeriatric co-management. The co-management model significantly shortened the length of stay in both acute and rehabilitation hospitals as well as improving functional outcomes on discharge from rehabilitation hospitals among those having hip surgery. These benefits were accrued at minimal additional cost.

Exposure to second-hand smoke is a known risk factor for reproductive health problems in pregnant women; sudden infant death syndrome, acute respiratory infections, ear infections, and asthma attacks in infants and children.[3] The World Health Organization recommends interventions to help expectant fathers quit smoking. Research targeting expectant fathers is scarce. Wang et al[4] evaluated the effect of a combination of brief advice, 1-week nicotine replacement therapy (patch or gum), and active referral to smoking cessation services on smoking cessation in 1053 smoking expectant fathers recruited from prenatal clinics of public hospitals in Hong Kong. They showed that biochemically validated abstinence (exhaled carbon monoxide) was significantly higher in expectant fathers who received the combination intervention, compared with those who received brief advice alone. The findings support provision of brief smoking cessation interventions to expectant fathers visiting prenatal clinics.

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# Serial real-time monitoring of circulating tumour cells and cell-free DNA in blood for prognosis of oesophageal carcinoma: abridged secondary publication

**ML Lung ***

**KEY MESSAGE**

Longitudinal serial real-time monitoring of circulating tumour cells and cell-free DNA in blood provides supplementary prognostic information for risk stratification of patients with advanced oesophageal squamous cell carcinoma. It has potential clinical utility for non-invasive monitoring of minimal disease burden to support clinical decision for early switch to next line therapies.

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HMRF project number: 05160926

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## Introduction

High mortality from cancers results from development of treatment-refractory metastasis. Thus, detecting metastatic disease early is important to improve treatment. Circulating tumour cells (CTCs) are 'seeds' for metastasis. They are shed from primary/metastatic tumours into the bloodstream and comprise only a minute fraction of the total blood cells. Advancements in identification of CTCs enables non-invasive real-time monitoring of tumour molecular heterogeneity and evolving drug resistance.

The incidence of oesophageal squamous cell carcinoma (OSCC) is highest among Chinese populations. OSCC ranks seventh in mortality among Hong Kong men. Patients with OSCC are usually diagnosed at a late stage, often with metastasis. Current treatment involves chemoradiotherapy (CRT) plus surgery. Many patients with distant metastasis die within 1 year of diagnosis. Even with neoadjuvant CRT, patients with locoregionally advanced OSCC die of recurrent disease within 5 years. Treatment for metastatic OSCC involves platinum plus fluoropyrimidine as first-line treatment and docetaxel as second-line treatment.

We isolated rare CTCs from bloods of patients with OSCC to determine their use as predictive biomarkers for cancer recurrence so as to enable timely clinical decisions and improve treatments and outcomes. Clinical significance of CTC enumeration versus computed tomography (CT) and/or positron emission tomography (PET) was examined. Next-generation sequencing (NGS) was used to determine tumour progression and evolution of chemoresistance. Identification of key driver genes for metastasis and druggable targets may provide the rationale for improved diagnosis and targeted treatment of metastatic OSCC.

## Methods

Patients with OSCC treated at Queen Mary Hospital between 2017 and 2020 were recruited. Their blood samples were collected for CTC enumeration. Patients with newly diagnosed OSCC underwent endoscopy with ultrasound and CT/PET. Patients with T3/4N+ disease without distant metastasis were treated with neoadjuvant CRT (with carboplatin+paclitaxel). Reassessment was performed after CRT; resectable tumours were surgically removed. Patients with metastasis underwent palliative CT. First-line treatment was platinum+fluoropyrimidine. Patients with responding or stable disease were treated for six cycles, whereas patients with progressive disease underwent alternative CT.

Blood samples were collected at diagnosis, during and after treatment, and at relapse. CTC enumeration was compared with initial/reassessment CT/PET scans. For locoregional disease, specimens taken before treatment were correlated with specimens taken at weeks 9 to 12 to assess early relapse. For metastatic OSCC, serial bloods were collected to determine the efficacy of CTCs as predictive biomarkers of CT response. Their results were correlated with imaging and reassessment results to determine CTC usefulness as predictors for second-line CT. For relapse disease, another CTC sample was taken for analysis. High CTC purity post-treatment was used for comparative NGS mutational profiling with pre-treatment specimens at diagnosis.

CTC enumeration was determined by immunofluorescence staining. The workflow has



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been reported in our previous studies.[1-3] NGS was used to determine CTC genomic mutations. Our established bioinformatics pipelines were used for analysis.[3] CTC enumerations were compared between patients and healthy volunteers. Kaplan-Meier and Cox regression analyses were used for survival association. Partial response is defined as ≥30% reduction in the sum of the longest diameter of all target lesions. The pathologic tumour regression grade is predictive of disease-free survival after neoadjuvant CRT in OSCC.[4] Longitudinal data were compared between groups.

Imaging analysis was based on internal references of standardised uptake values. PET parameters (maximum standardised uptake value, metabolic tumour volume, and total lesion glycolysis) were computed. Lesions were categorised with the TNM staging system. Treatment responses were evaluated with RECIST and PRECIST criteria.

## Results

In 57 patients (median age, 63 years; 86% were male) with locally advanced stage III-IV OSCC who received palliative platinum-based CT, the median time to progression at interim reassessment, progression-free survival (PFS), and overall survival (OS) were 74.5, 94, and 181 days, respectively, whereas 56%, 90%, and 70% of patients relapsed at interim reassessment, had disease progression, and died, respectively.

Baseline, pre-cycle III, post-cycle IV, end of CT, and relapse CTC enumeration data were obtained for 55, 45, 12, 14, and 11 patients with advanced OSCC, respectively. Frequencies of patients with detectable CTCs were 70.9%, 55.6%, 66.7%, 42.9%, and 54.5%, respectively. The median cell-free DNA (cfDNA) levels were 3123, 2176, 3092, 1579, and 3095 copies of haploid genome, respectively.

The mean CTC enumeration was 2.31 and 2.47 cells/5 mL blood at baseline and pre-cycle III, respectively. A cut-off point of ≥3 was chosen to examine its predictive value. Patients with ≥3 CTCs at end of cycle II had significantly higher risk of progression at interim reassessment and worse PFS and OS, compared with those with 0 to 2 CTCs (Table). Patients with 0 to 2 CTCs (low risk) had significant longer time to progression at interim reassessment and longer PFS and OS, compared with those with intermediate risk (other CTC changes) or high risk (≥3 CTCs). Patients with unfavourable changes of both high cfDNA1 (≥3.360) and cfDNA2 (≥3.2817) were categorised as high risk; others were low risk. Patients with favourable changes had significant longer OS, compared with those with unfavourable change.

Patients were categorised into four risk groups based on integration of changes of both CTC1/CTC2 and cfDNA1/cfDNA2 levels from baseline to pre-cycle III. Each specimen was categorised into high (1 mark) and low (0 mark) groups. Patients with two favourable changes were categorised as low risk (0 mark). Patients with two unfavourable changes were categorised as high risk (3 marks) and at risk (2 marks), respectively. Other combinations were categorised as at risk (1 mark). Patients in low-risk group had significantly longer time of progression, PFS, and OS, compared with other groups. CTC enumeration is useful for longitudinal serial monitoring of disease progression. Clinical assessment and PET detected disease progression with a 6-month lag time, after dramatic increase of the cfDNA level and tumour-specific somatic mutations including *TP53* mutation frequency and *MET* amplification.

In multivariate regression analysis, CTC count of ≥3 at pre-cycle III was the independent predictor for shorter time to progression at interim reassessment, whereas CTC count of ≥3 at pre-cycle III and having primary tumour resected at blood collection were independent predictors for shorter PFS, whereas age and combined unfavourable changes of CTC1/2 and cfDNA1/2 were independent predictors for shorter OS (Table).

In 37 patients with locoregionally advanced OSCC who received curative CRT/surgery (n=33) or CRT without surgery (n=4), those with ≥3 CTCs at the end of CRT/pre-operation had higher risk of early progression (hazard ratio=5.859, P=0.031), compared with those with 0-2 CTCs.

In 50 patients with advanced OSCC who received palliative CT, the percentage of usable bases on target for the buffy coat DNAs and CTC samples were 48% and 43% with mean target coverage of 1708 and 1470, respectively. Serial NGS analysis identified seven genes to be associated with poorer OS. Patients with positive mutation signature were associated with shorter OS and PFS.

## Conclusion

CTC count at pre-cycle III is the independent predictor for time to progression at interim reassessment and PFS. Combined changes of CTC count and cfDNA level from baseline to pre-cycle III are independent predictors for OS. Baseline and pre-cycle III liquid biopsy can identify patients with advanced OSCC at increased risk of early-disease progression, treatment failure, and death. Prospective serial longitudinal monitoring of CTCs and cfDNAs in patients with advanced OSCC is recommended.

## Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#05160926). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

TABLE. Circulating tumour cells (CTC) counts and cell-free DNA (cfDNA) levels at baseline and two cycles of chemotherapy (pre-cycle III) as predictors of time to progression at interim reassessment, progression-free survival, and overall survival

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Hazard ratio (95% confidence interval) | P value | Hazard ratio (95% confidence interval) | P value |
| Time to progression at interim reassessment (n=52) | | | | |
| Age | 1.003 (0.95-1.06) | 0.906 | - | - |
| Stage at blood collection: IV vs III (ref) | 0.262 (0.11-0.62) | **0.002** | - | - |
| Lymph node metastasis: yes vs no (ref) | 0.392 (0.18-0.84) | **0.016** | - | - |
| Baseline CTC count: ≥3 vs 0-2 (ref) [n=50] | 2.072 (0.87-4.95) | 0.101 | - | - |
| Pre-cycle III CTC count: ≥3 vs 0-2 (ref) [n=42] | 3.426 (1.32-8.87) | **0.011** | 3.426 (1.32-8.87) | **0.011** |
| Baseline log cfDNA (n=39) | 4.980 (0.91-27.22) | 0.064 | - | - |
| Pre-cycle III log cfDNA (n=35) | 2.241 (0.77-6.53) | 0.139 | - | - |
| Progression-free survival (n=54) | | | | |
| Age | 0.956 (0.91-1.00) | 0.062 | - | - |
| Previous treatment: yes vs no (ref) | 0.561 (0.30-1.05) | 0.071 | - | - |
| Stage at blood collection: IV vs III (ref) | 0.430 (0.22-0.85) | **0.016** | - | - |
| Primary tumour resected at blood collection: yes vs. no (ref) [n=51] | 0.373 (0.19-0.75) | **0.005** | 0.402 (0.19-0.87) | **0.02** |
| Metastasis: yes vs no (ref) [n=40] | 0.517 (0.25-1.08) | 0.080 | - | - |
| Liver metastasis: yes vs no (ref) | 0.449 (0.21-0.98) | **0.043** | - | - |
| Baseline CTC count: ≥3 vs 0-2 (ref) [n=52] | 1.349 (0.69-2.63) | 0.380 | - | - |
| Pre-cycle III CTC count: ≥3 vs 0-2 (ref) [n=43] | 3.680 (1.73-7.81) | **0.001** | 4.014 (1.81-8.88) | **0.001** |
| Baseline log cfDNA (n=47) | 1.959 (0.67-5.76) | 0.222 | - | - |
| Pre-cycle III log cfDNA (n=40) | 1.681 (0.70-4.06) | 0.249 | - | - |
| Overall survival (n=57) | | | | |
| Age | 0.940 (0.89-0.99) | **0.027** | 0.932 (0.87-0.99) | **0.032** |
| Previous treatment: yes vs no (ref) | 0.534 (0.28-1.02) | 0.056 | - | - |
| Baseline CTC count: ≥3 vs 0-2 (ref) [n=55] | 0.973 (0.44-2.14) | 0.946 | - | - |
| Pre-cycle III CTC count: ≥3 vs 0-2 (ref) [n=45] | 3.576 (1.63-7.84) | **0.001** | - | - |
| Baseline log cfDNA (n=48) | 8.338 (2.42-28.7) | **0.001** | - | - |
| Pre-cycle III log cfDNA (n=41) | 5.451 (1.74-17.1) | **0.004** | - | - |
| Change of cfDNA1/2 (n=40) | | | | |
| Two favourable changes with 0-1 mark (other combinations) [n=21] | Reference | - | - | |
| One favourable change with 1-3 marks (high cfDNA1 & cfDNA2) [n=19] | 4.444 (1.85-10.68) | **0.001** | | |
| Change of CTC1/2 (n=43) | | | | |
| Two favourable changes with 0-1 mark (low CTC1 & CTC2) [n=22] | Reference | **0.012** | - | - |
| One favourable change with 1-3 marks (other combinations) [n=16] | 3.103 (1.11-8.65) | 0.089 | | |
| Two unfavourable changes with 3 marks (high CTC1 & CTC2) [n=5] | 6.178 (1.87-20.4) | **0.004** | | |
| Combined changes of CTC and cfDNA (n=44) | | | | |
| Two favourable changes with 0-1 mark (n=12) | Reference | **0.001** | | **0.002** |
| One favourable change with 1-3 marks (n=22) | 3.103 (1.11-8.65) | **0.030** | 6.008 (1.27-28.5) | **0.024** |
| Two unfavourable changes with 3 marks (n=8) | 6.178 (1.87-20.4) | **0.003** | 9.520 (1.81-50.0) | **0.008** |
| Two unfavourable changes with 4 marks (n=2) | 53.07 (7.02-401) | **$1.2 \times 10^{-4}$** | 81.958 (7.95-845) | **$2.2 \times 10^{-4}$** |

## Disclosure

The results of this research have been previously published in:

1. Ko JMY, Ng HY, Lam KO, et al. Liquid biopsy serial monitoring of treatment responses and relapse in advanced esophageal squamous cell carcinoma. Cancers (Basel) 2020;12:1352.
2. Ko JMY, Lam KO, Kwong DLW, et al. Circulating tumor cell enumeration for serial monitoring of treatment outcomes for locally advanced esophageal squamous cell carcinoma. Cancers 2023;15:832.

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# Health economic analysis of epidermal growth factor receptor mutation-guided first-line therapies for advanced non-small-cell lung cancer: abridged secondary publication

**JHS You *, WCS Cho, YC Li, CK Kwan, JSK Au**

## KEY MESSAGES

1. *EGFR* mutation-guided use of tyrosine kinase inhibitor (TKI) therapy (afatinib, erlotinib and gefitinib) appears to gain higher quality-adjusted life-years than empirical chemotherapy (without *EGFR* mutation testing).
2. The cost-effectiveness of *EGFR* mutation-guided TKI is highly subject to the cost of TKI therapy and the willingness-to-pay threshold.

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## Introduction

In Hong Kong, lung cancer is the second most common cancer, with the highest mortality (crude rate, 52.6 per 100 000 persons) among the top 10 cancers.[1] Approximately 85% to 90% of lung cancers are classified as non-small-cell lung cancer (NSCLC), and approximately 80% of NSCLC are diagnosed in advanced stage of IIIB/IV. Standard platinum-based chemotherapy for advanced NSCLC can modestly lengthen survival by a few months.

Epidermal growth factor receptor (*EGFR*) gene mutations are actionable targets in NSCLC.[2] These mutations are correlated with treatment response to tyrosine kinase inhibitor (TKI) therapy. This study aims to compare the *EGFR* mutation-guided use of afatinib, erlotinib, and gefitinib versus empirical chemotherapy as first-line treatment of advanced NSCLC in Hong Kong.

## Methods

A Markov model was designed to simulate outcomes of a hypothetical cohort of advanced (stage IIIB/IV) NSCLC adult patients with untested *EGFR*-sensitising mutation status (Fig 1). Four treatment strategies were evaluated: empirical first-line chemotherapy and *EGFR* mutation-guided use of afatinib, erlotinib, and gefitinib. The model time horizon was 10 years (with monthly cycle), and outcome measures were direct medical cost, progression-free survival, life-years, and quality-adjusted life-years (QALYs)

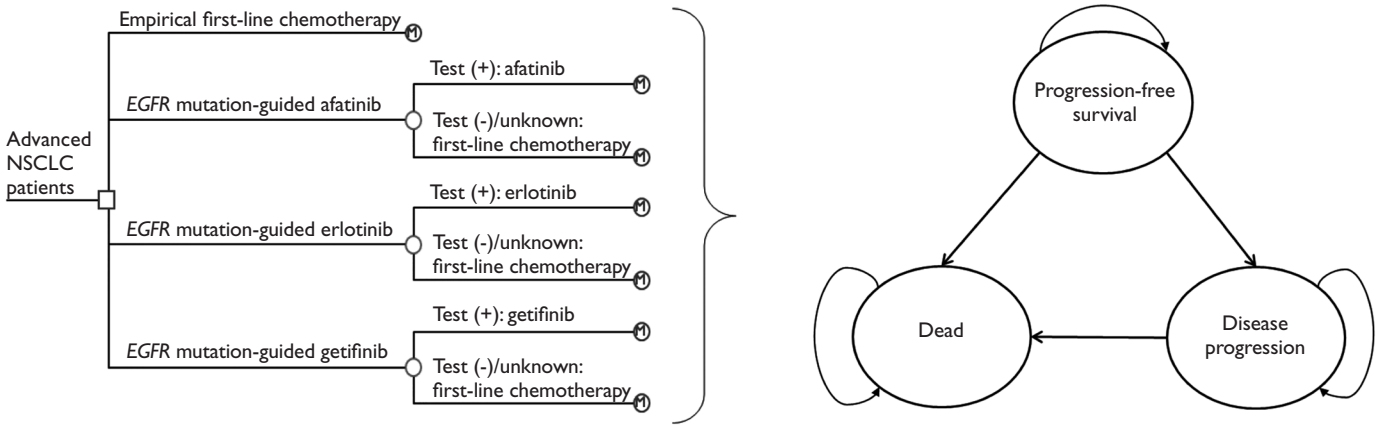


FIG 1. Simplified Markov model of empirical chemotherapy as well as epidermal growth factor receptor (*EGFR*) mutation-guided afatinib, erlotinib, and gefitinib therapies for advanced non-small-cell lung cancer (NSCLC)



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gained by each treatment strategy.

The literature on MEDLINE over the period 2000 to 2020 was searched using keywords: advanced non-small-cell lung cancer, NSCLC, *EGFR* mutation, overall survival, progression-free survival, first-line treatment, first-line chemotherapy, gefitinib, erlotinib, and afatinib. Selection criteria of clinical trials were: (1) in English language, (2) adult patients with stage IIIB/IV NSCLC, and (3) provision of progression-free survival, overall survival or adverse event rates.

The QALYs expected by each subject was estimated from cumulative subject-time spent in a heath state and the health state-specific utility value. The health states included progression-free survival, disease progression, and death, further adjusted with disutility of treatment-related serious adverse events (SAEs). The QALY gained was discounted by an annual rate of 3%.

Health economic analysis was conducted on direct medical costs from the perspective of Hong Kong public healthcare provider. Healthcare resource utilisation during progression-free survival and disease progression was estimated retrospectively. Medical record review was conducted for 400 patients aged ≥18 years with diagnosis of advanced (stage IIIB/IV) NSCLC who were treated with first-line chemotherapy (n=200, 58% male, mean age 67±12 years) or TKI (n=200, 56% male, mean age 66±12 years) in 2013 to 2017 at Queen Elizabeth Hospital and United Christian Hospital. Healthcare resource utilisation was collected to estimate monthly direct medical costs for progression-free survival state and disease progression state, and management cost per episode of treatment-related SAEs. The costs accumulated were discounted with an annual rate of 3%.

Base-case analysis compared the expected direct medical cost and QALYs of each *EGFR* mutation-guided TKI therapy with those of the empirical chemotherapy. A treatment strategy was dominated when it gained lower QALYs at higher cost than another option, and the dominated option was eliminated from further cost-effectiveness analysis. If a treatment strategy gained additional QALYs at higher cost than another alternative, incremental cost-effectiveness ratio (ICER) of the more effective strategy was calculated: ICER=Δcost/ΔQALYs.

The World Health Organization recommends that ICER <1× gross domestic product (GDP) per capita is highly cost-effective and <3× GDP per capita is cost-effective. The GDP per capita of Hong Kong was USD47 812 in 2019 and thus USD143 436 (3× GDP per capita) was used as the willingness-to-pay (WTP) threshold in the base-case analysis. A treatment alternative was preferred if it was effective in saving QALYs at lower cost or if it was effective in saving QALYs at higher cost and the ICER was below WTP threshold.

Sensitivity analysis was performed by TreeAge Pro 2020 to examine the robustness of the model results. One-way and probabilistic sensitivity analyses and scenario analysis were conducted.

## Results

*EGFR* mutation-guided use of all three TKIs (afatinib, erlotinib, gefitinib) gained higher QALYs than empirical chemotherapy (Table). Compared with empirical chemotherapy, *EGFR* mutation-

TABLE. Base-case analysis for empirical chemotherapy as well as epidermal growth factor receptor (*EGFR*) mutation-guided afatinib, erlotinib, and gefitinib therapies for advanced non-small-cell lung cancer

| Base-case analysis | Empirical chemotherapy | *EGFR* mutation-guided erlotinib therapy | *EGFR* mutation-guided gefitinib therapy | *EGFR* mutation-guided afatinib therapy |
|---|---|---|---|---|
| Direct costs, USD | 21 355 | 18 487 | 25 760 | 35 570 |
| Progression-free survival, mo | 8.67 | 15.78 | 14.30 | 16.79 |
| Overall survival, mo | 33.30 | 34.18 | 30.98 | 34.50 |
| Quality-adjusted life-years (QALYs) | 1.6358 | 1.8072 | 1.6464 | 1.8388 |
| Versus empirical chemotherapy | | | | |
| Incremental cost, USD | - | -2868 | 4405 | 14 215 |
| Incremental QALYs | - | 0.1714 | 0.0106 | 0.2030 |
| incremental cost-effectiveness ratio, USD per QALY | - | Dominating empirical therapy | 415 566 | 70 025 |
| Versus the next less costly strategy | | | | |
| Incremental cost, USD | 2868 | - | 7273 | 17 083 |
| Incremental QALYs | -0.1714 | - | -0.1608 | 0.0316 |
| Incremental cost-effectiveness ratio, USD per QALY | Dominated by *EGFR* mutation-guided erlotinib therapy | - | Dominated by *EGFR* mutation-guided erlotinib therapy | 540 601 |

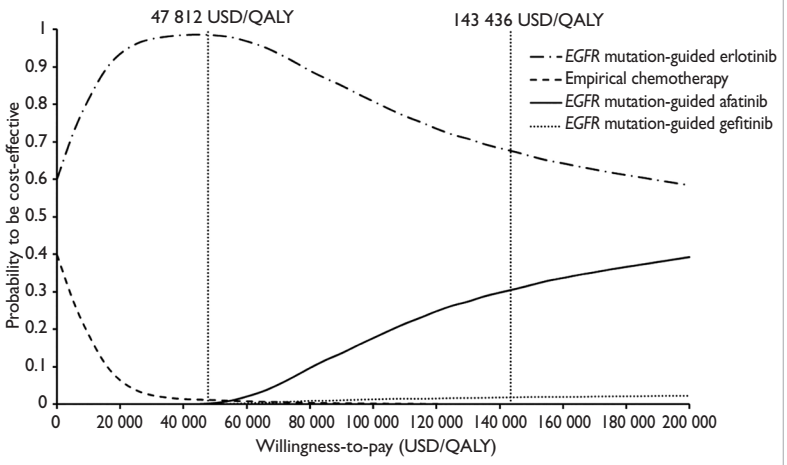


FIG 2. Acceptability curves of empirical chemotherapy as well as epidermal growth factor receptor (*EGFR*) mutation-guided afatinib, erlotinib, and gefitinib therapies for advanced non-small-cell lung cancer (NSCLC) to be cost-effective against willingness-to-pay in USD/quality-adjusted life-years (QALY)

guided erlotinib gained higher QALYs with cost-saving, and the ICER of afatinib was lower than WTP threshold (143 436 USD/QALY). Both strategies of *EGFR* mutation-guided erlotinib and afatinib were cost-effective. *EGFR*-guided gefitinib gained higher QALY than empirical chemotherapy at an ICER (415 566 USD/QALY) exceeding WTP.

One-way sensitivity analysis found the base-case results robust to the variation of all model inputs. The *EGFR* mutation-guided afatinib therapy gained the highest QALYs with ICER exceeding the WTP threshold. The monthly cost of afatinib therapy was examined in extended one-way sensitivity analysis from the base-case value to a lower limit for identification of threshold value. The ICER of *EGFR* mutation-guided afatinib therapy became lower than the WTP threshold (and cost-effective) when the monthly cost of afatinib therapy was reduced by 56%. There was no threshold cost for EGFR mutation-guided gefitinib therapy because it was less effective.

In probabilistic sensitivity analysis with 10 000 Monte Carlo simulations, the acceptability of four treatment arms was examined simultaneously. Probabilities of each treatment strategy to be accepted as cost-effective are showed in the acceptability curves over a wide range of WTP (0-200 000 USD/QALY) [Fig 2].

*EGFR* mutation-guided therapies of afatinib, erlotinib, and gefitinib as well as empirical chemotherapy were accepted to be preferred strategy in 0.13%, 98.63%, 0.01%, and 1.23% of time at WTP 47 812 USD/QALY (1× GDP per capita), and in 30.54%, 67.54%, 1.79%, and 0.13% of time at WTP 143 436 000 USD/QALY (3× GDP per capita), respectively.

Two scenarios were examined. In scenario 1, public payer's perspective was applied on self-financed drugs (not subsidised by public payer). *EGFR* mutation-guided erlotinib therapy was preferred, with highest probability to be cost-effective when the WTP threshold was <81 470 USD/QALY. In scenario 2, a fifth study arm was added to examine *EGFR* mutation-guided TKI as the downstream treatment for patients who progressed on first-line empirical chemotherapy. *EGFR* mutation-guided erlotinib therapy was preferred, with highest probability to be cost-effective throughout the variation of WTP.

## Discussion

A cost-effectiveness analysis of afatinib, gefitinib, or erlotinib therapy and first-line chemotherapy for *EGFR* mutation-positive NSCLC patients was reported in China.[3] The QALY gain was highest with afatinib, followed by erlotinib, gefitinib, and chemotherapy. Our findings on the highest QALY gain by the afatinib therapy are consistent with those reported in China. In the present study, erlotinib therapy was accepted to be cost-effective (versus afatinib therapy). This was likely due to the difference in pricing of TKIs in Hong Kong and China.

The *EGFR* testing-guided use of TKI has been reported to be cost-effective in the literature when individual TKI strategy is compared with empirical chemotherapy. In cost-effectiveness analyses on *EGFR*-testing guided afatinib (in China) and erlotinib (in South Korea) versus empirical use of first-line chemotherapy, *EGFR*-mutation guided TKIs are reported to be cost-effective strategies.[4,5] In the present study, we showed consistent cost-effective acceptance of *EGFR*-mutation guided erlotinib and afatinib therapies versus empirical chemotherapy. *EGFR*-testing guided erlotinib therapy was the preferred cost-effective strategy in Hong Kong.

There are some limitations to the present study. The model simplified real-life events of advanced NSCLC therapy. We included SAEs of TKI and chemotherapy, yet the impact of less SAEs were not fully represented. Only English-language publications were included, but relevant findings reported in other language (such as Chinese language) were not included in the present model. Loss of productivity was not included and might therefore underestimate the impact of NSCLC treatment on indirect cost.

## Conclusion

*EGFR* mutation-guided use of afatinib, erlotinib, and gefitinib appear to gain higher QALYs than empirical chemotherapy (without *EGFR* mutation testing). *EGFR* mutation-guided erlotinib therapy seems to be the most cost-effective from the perspective of public healthcare provider in Hong Kong.

## Funding

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## Disclosure

The results of this research have been previously published in:

1. You JHS, Cho WCS, Ming WK, et al. *EGFR* mutation-guided use of afatinib, erlotinib and gefitinib for advanced non-small-cell lung cancer in Hong Kong: a cost-effectiveness analysis. PLoS One 2021;16:e0247860.

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# Psychometric evaluation of the Chinese version of the Resilience Scale for Children: abridged secondary publication

JOK Chung *, WHC Li, GCF Chan, SY Chiu, KY Ho

KEY MESSAGES

1. The Chinese version of the 10-item Resilience Scale for Children (RS-10) is a reliable and valid tool to assess resilience among Hong Kong Chinese children with cancer.
2. The Chinese version of the RS-10 can be used to evaluate the effectiveness of nursing interventions to enhance resilience and promote mental well-being among children with cancer.
3. Confirmatory factor analysis confirms the two-factor structure of the Chinese version of RS-10.

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## Introduction

Resilience is associated with positive mental health outcomes in children and adolescents such as reduced levels of anxiety, depression, and obsessive-compulsive symptoms.[1] Assessment of responses to stress and adversity in children with cancer may help design appropriate psychological interventions to enhance resilience of children and foster development of coping mechanisms and positive mental well-being. Most studies have focused on promoting resilience in parents, caregivers, or other family members of children with cancer.

The 25-item Resilience Scale was developed by Wagnild and Young,[2] based on a conceptual model derived from a qualitative study of women who exhibited adaptation after a major life event. Subsequently, the 10-item Resilience Scale for Children (RS10) was developed to measure children's capacity to respond to life changes.[3] The RS10 is positively worded and easily understood by children as young as 7 years old and has been translated from English into Arabic and Swedish. This study aims to translate the RS-10 to Chinese and evaluate its linguistic and cultural equivalence as well as its psychometric properties.

## Methods

Children aged 7 to 14 years who were diagnosed with cancer within the previous 6 months and under active treatment were recruited from the paediatric oncology units of Queen Mary Hospital and Hong Kong Children's Hospital in Hong Kong. Children younger than 7 years may have limited verbal and cognitive capacities were excluded, as were children with cognitive and learning problems.

Participants were asked to respond to the Chinese version of RS-10, Center for Epidemiologic Studies Depression Scale for Children (CES-DC), and the Rosenberg's Self-Esteem Scale (RSES).

A panel of experts was set up to test the semantic and content equivalence of the Chinese version of the RS-10. For semantic equivalence, the panel rated each item in a four-point scale from 1 (not equivalent) to 4 (most equivalent). Any item that was considered not equivalent (being rated 1 or 2 by >20% of respondents) was amended. For content equivalence, the panel rated each item in a 4-point scale from 1 (not relevant) to 4 (very relevant).

Convergent validity was determined by correlations between scores on the Chinese versions of the RS-10 and the RSES. Discriminant validity was determined by correlation between scores on the RS-10 and the CES-DC.

Factorial validity was evaluated by confirmatory factor analysis. The Tucker-Lewis index, root-mean-square error of approximation, comparative fit index, goodness-of-fit index, and standardised root-mean-square residual were used to evaluate the goodness of fit, with cut-off values being ≥0.95, ≤0.06, ≥0.95, ≥0.90, and ≤0.08, respectively.[4] The diagonally weighted least square estimator was used to assess the ordinal variables in the RS-10, with values of 0.32, 0.45, 0.55, 0.63, and 0.71 indicating poor, fair, good, very good, and excellent factor loadings, respectively. Items with factor loadings of <0.40 were removed. Initial one-factor and two-factor model analyses were performed using the Analysis of Moment Structures software.[5]

Reliability of the Chinese version of the



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RS-10 was determined by its internal consistency (Cronbach's α). Participants were asked to respond to the RS-10 again after 2 weeks via telephone. The intraclass correlation coefficient was used to estimate the test-retest reliability coefficient.

## Results

A total of 100 boys and 86 girls (mean age, 10.4±2.5 years) were recruited. 20 (10.8%) participants were from single-parent families. The most common diagnosis was leukaemia (46.2%), followed by brain tumour (23.1%). 58.6% of the participants received chemotherapy only, whereas 36.5% received more than one cancer treatment.

The semantic equivalence of the items in the Chinese version of the RS-10 ranged from 86% to 100% indicating high equivalence to those in the original version. The content validity index was 96% indicating validity. Thus, no item of the Chinese version of the RS-10 required modification.

The Chinese version of the RS-10 was negatively correlated with the CES-DC ($r$= -0.52, P=0.01) and positively correlated with the RSES ($r$=0.61, P=0.01). This indicates that greater resilience was associated with fewer self-reported depressive symptoms and higher levels of self-esteem. Thus, convergent and divergent validity of the Chinese version of the RS-10 were supported.

In confirmatory factor analysis, factor loadings ranged from 0.51 to 0.79, with positive correlations between parameters (Fig). The modified two-factor model performed well across all fit indices: Chi-square divided by degrees of freedom=2.34, Tucker-Lewis index=0.951, root-mean-square error of approximation=0.053, comparative fit index=0.962, goodness-of-fit index=0.948, and standardised root-mean-square residual=0.052 (Table). The factor structure of the Chinese version of the RS-10 and the observed data were good fit.

The intraclass correlation coefficient of the Chinese version of the RS-10 at 2-week intervals was 0.89, whereas the internal consistency was confirmed by a Cronbach's α of 0.83. The corrected item-total correlation coefficients ranged from 0.38 to 0.61. All items correlated with the total score on the scale.

## Discussion

The Chinese version of the RS-10 has good internal consistency and test-retest reliability, excellent content validity, and appropriate convergent and discriminant validity. The two-factor structure is supported. The Chinese version of the RS-10 can be used to assess and monitor levels of resilience in Hong Kong Chinese children with cancer. As resilience can prevent development of mental health problems and promote positive mental health outcomes, appropriate psychological interventions are recommended to enhance resilience of children with cancer and foster coping mechanisms and positive mental well-being.

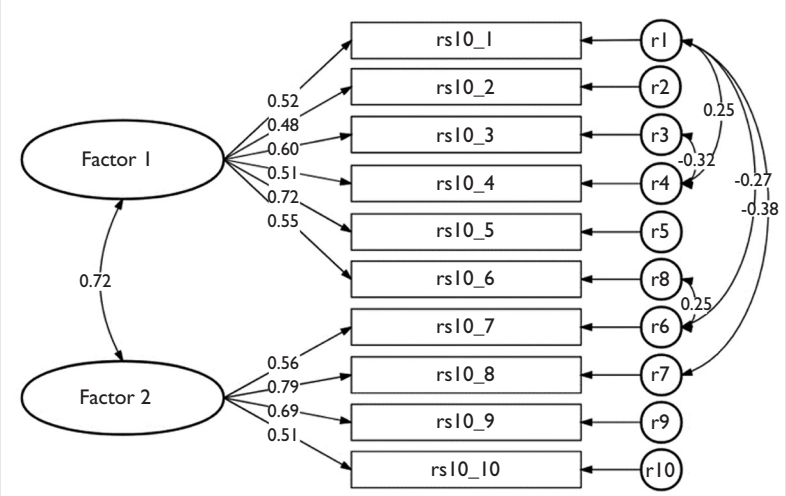


FIG. Confirmatory factor analysis for the two-factor structure model of the Chinese version of the 10-item Resilience Scale for Children

TABLE. Fit statistics for the factor structure models of the Chinese version of RS-10

| | $\chi^2$ | Degree of freedom | $\chi^2$/degree of freedom | Tucker-Lewis index | Root-mean-square error of approximation | Comparative fit index | Goodness-of-fit index | Standardised root-mean-square residual |
|---|---|---|---|---|---|---|---|---|
| One-factor model | | | | | | | | |
| Initial | 179.793 | 35 | 5.137 | 0.622 | 0.151 | 0.706 | 0.834 | 0.096 |
| Modified | 83.042 | 29 | 2.864 | 0.830 | 0.101 | 0.890 | 0.920 | 0.070 |
| Two-factor model | | | | | | | | |
| Initial | 136.668 | 34 | 4.02 | 0.724 | 0.129 | 0.792 | 0.876 | 0.085 |
| Modified | 62.443 | 28 | 2.34 | 0.951 | 0.053 | 0.962 | 0.948 | 0.052 |
| Cut-off value | | | | ≥0.95 | ≤0.06 | ≥0.95 | ≥0.90 | ≤0.08 |

## Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#15163011). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

## Disclosure

The results of this research have been previously published in:

1. Chung JOK, Li WHC, Wei X, Cheung AT, Ho LLK, Chan GC. Translation and psychometric evaluation of the Chinese version of the resilience scale for children with cancer. Health Qual Life Outcomes 2021;19:232.

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# Orthogeriatric co-management model to improve outcome and cost-effectiveness of fragility hip fractures: abridged secondary publication

**KL Leung *, TW Lau, HW Chan, KC Chiu, CX Fang, YH Lam, KH Yee, CY Tsang**

## KEY MESSAGES

1. The orthogeriatric co-management model significantly shortens the length of stay in both acute and rehabilitation hospitals among geriatric patients with fragility hip fractures.
2. The orthogeriatric co-management model significantly improves functional outcomes on discharge from the rehabilitation hospital among geriatric patients who underwent surgery for fragility hip fractures.
3. Benefits of the model are achieved at minimal additional cost.

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## Introduction

Geriatric hip fractures are common fragility fractures in Hong Kong. In 2007, a geriatric hip fracture clinical pathway was adopted to address the escalating needs of the community.[1] The pathway has shown to shorten the length of stay by 6.1 days in acute hospitals (and hence improve clinical outcomes including pneumonia) and decrease the average manpower cost per hip fracture case.

The average age of our patients with hip fracture is 84 years; many have multiple comorbidities and polypharmacy problems. These patients require considerable support during early postoperative period and after discharge to prevent deterioration of physical and mental health that may lead to repeated hospital readmissions and prolonged hospital stays.

Since November 2018, a new orthogeriatric co-management model, with a geriatrician involving in daily management in both acute and rehabilitation phases, has been implemented to improve the outcome and cost-effectiveness of the management process.

## Methods

Data of geriatric hip fracture patients from 1 April 2018 to 30 October 2018 under the conventional orthopaedic care model were compared with data of geriatric hip fracture patients from 1 February 2019 to 31 August 2019 under the orthogeriatric co-management model. Efficiency was reflected by the total length of stay in acute and convalescence hospitals.

## Results

Of 401 eligible patients, 194 received conventional orthopaedic care and 207 received orthogeriatric co-management (Table 1). The mean age of patients was 84.2 years; 290 (72.3%) patients were female; 217 (54.1%) patients had femoral neck fractures and 178 (44.4%) patients had pertrochanteric fractures.

Under the orthogeriatric co-management model, the median length of stay in acute and rehabilitation hospitals decreased by 1 day and 2 days, respectively (P=0.001). The orthogeriatric co-management model was associated with higher median modified Barthel Index on discharge from the rehabilitation hospital (81 vs 63.5, P<0.001). Linear regression model showed all variables (orthogeriatric co-management model, modified Barthel Index on admission to rehabilitation hospital, and abbreviated mental test score) predicted modified Barthel Index on discharge from rehabilitation hospital: $F(3, 158)=69.275$, $P<0.001$, $R^2=0.568$ (Table 2). All three variables added significantly to the prediction.

More patients under the orthogeriatric co-management model were prescribed osteoporosis medications within 1 year after the index fracture (66.7% vs 12.9%, P<0.001). There was no significant difference between the two models in terms of the 28-day unplanned readmission rate, complication rate, mortality rate, and Elderly Mobility Scale score on discharge from the rehabilitation hospital. The cost per episode of hip fracture was similar between the two models.



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TABLE 1. Geriatric fracture hip patients under conventional model and orthogeriatric model

| | Conventional (n=194)* | Orthogeriatric (n=207)* | P value |
|---|---|---|---|
| Age, y | 84.8±7.6 | 83.6±8.2 | 0.165 |
| Sex | | | 0.704 |
| Male | 52 (26.8) | 59 (28.5) | |
| Female | 142 (73.2) | 148 (71.5) | |
| Abbreviated mental test score on admission | 5.1 (5.8) | 7 (8.1) | 0.079 |
| Modified Barthel Index on admission to rehabilitation hospital | 48 (24) | 49 (27) | 0.055 |
| Pre-morbid residence | | | 0.042 |
| Old age home | 53 (27.3) | 38 (18.4) | |
| Home | 141 (72.7) | 169 (81.6) | |
| Pre-morbid mobility | | | 0.581 |
| Unaided | 61 (31.4) | 69 (33.3) | |
| With aids | 121 (62.4) | 124 (59.9) | |
| Chairbound | 11 (5.7) | 10 (4.8) | |
| Bedbound | 1 (0.5) | 4 (1.9) | |
| Fracture site | | | 0.127 |
| Neck of femur | 97 (50.0) | 120 (58.0) | |
| Pertrochanteric | 94 (48.4) | 84 (40.6) | |
| Surgery | | | 0.149 |
| Replacement | 65 (33.5) | 84 (40.6) | |
| Fracture fixation | 129 (66.5) | 123 (59.4) | |
| Charlson comorbidity index | 2 (5) | 2 (5) | 0.129 |
| Preoperative haemoglobin level, g/dL | 11.4±1.8 | 11.6±1.9 | 0.387 |
| Preoperative albumin level, g/L | 38.9±3.9 | 39.2±4.3 | 0.449 |

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

TABLE 2. Linear regression analysis for predictors of modified Barthel Index on discharge from rehabilitation hospital

| Predictor | Unstandardised coefficient (B) [95% confidence interval] | P value |
|---|---|---|
| Group (orthogeriatric model vs conventional model) | 5.37 (0.23-10.51) | 0.04 |
| Abbreviated mental test score | 2.23 (1.40-3.06) | <0.001 |
| Modified Barthel Index on admission to rehabilitation hospital | 0.57 (0.42-0.71) | <0.001 |

## Discussion

In the conventional model, the geriatric consultative service is on request of the orthopaedic surgeon in charge. Thus, there is a time lag for patients to be seen by the geriatrician. In the orthogeriatric co-management model, patients are co-managed by both the orthopaedic surgeon and the geriatrician. Joint ward rounds are up to 3 times weekly to enable earlier detection of medical problems and timely intervention. The orthopaedic surgeon and geriatrician deliberate the optimal plan of medical treatment in unison. Patients were transferred from acute hospital to rehabilitation hospital earlier because of the enhanced geriatrician support in the rehabilitation hospital.

Discharging patients prematurely may be detrimental to patient health. It is important to ensure proper rehabilitation is achieved prior to discharge of patients. Both conventional and orthogeriatric models had similar unplanned readmission rates and mortality. Reductions in length of stay in acute and rehabilitation hospitals were due to the new measures in the orthogeriatric model that eliminated unnecessary delays in decision making.

Patients need a safe, quick, and efficient recovery to return to their normal lives after surgery.

A multidisciplinary management programme can help to speed up functional recovery.[2] In the present study, the modified Barthel Index on discharge from the rehabilitation hospital was significantly higher under the orthogeriatric model than under the conventional model. This is consistent with one study that reported significant improvement in Functional Independence Measure motor and cognitive scores under a comprehensive orthogeriatric approach, with the rate of successful rehabilitation doubled.[3] An accelerated rehabilitation study reported an increase in the activities for daily living score and a reduction in the length of hospital stay.[4] Prolonged bed rest and patient immobility is known to be associated with functional decline in activities of daily living and increased complications and mortality.

The conventional care model lacks formal osteoporosis management in the pathway. A more holistic approach to patients with hip fractures is important.[5] In the orthogeriatric co-management model, geriatricians may initiate osteoporosis treatment while the patient is still in the rehabilitation hospital. Follow-up of osteoporosis treatment is continued even after discharge to the geriatric clinic, where education and fall prevention programmes are provided by nurses. All these help reduce the risk of future fractures. In the present study, subsequent fractures within 1 year of index fracture reduced (but not significantly) under the orthogeriatric model (1.4% vs 3.1%, P=0.27). We anticipate that the effect of osteoporosis management will become more apparent over a longer period.

There was a decreasing trend for 3-, 6-, and 12-month mortality under the orthogeriatric co-management model. We are unable to conclude whether the study was underpowered to detect changes in mortality, because power analysis was calculated based on length of stay.

Cost per episode was similar between the conventional and orthogeriatric models. The decreased cost from acute hospitals was offset by the increased cost in rehabilitation hospitals. The decreased length of stay resulted in decreased total inpatient bed days for geriatric hip fractures and a decreased ratio of geriatric hip fracture among orthopaedics overall inpatient bed days. However, there was a shortage of manpower in the rehabilitation hospital during the conventional model owing to staff turnover. This shortage was recovered next year with new recruits when the orthogeriatric model was running.

In Hong Kong public healthcare system, the number of medical staff is determined by the annual government budget, and hardware (medication, implants, prostheses, and consumables) is bulk purchased by the hospital management. After implementation of the orthogeriatric model, the only additional resource is the increase in geriatrician manpower. Inpatient length of stay has been used as the cost-effectiveness measure in the Hospital Authority. The cost per patient day in hospital (acute and rehabilitation) was estimated to be $6310 in 2021/22. Reduction in length of stay in both acute and rehabilitation hospitals is likely to improve cost-effectiveness.

## Conclusion

Geriatric hip fractures are a major burden to the healthcare system. The orthogeriatric co-management model for geriatric patients with hip fracture is effective in shortening the total length of stay in acute and rehabilitation hospitals and in improving functional outcomes of patients. Such benefits are achieved at minimal additional cost.

## Funding

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## Disclosure

The results of this research have been previously published in:

1. Yee DKH, Lau TW, Fang C, Ching K, Cheung J, Leung F. Orthogeriatric multidisciplinary co-management across acute and rehabilitation care improves length of stay, functional outcomes and complications in geriatric hip fracture patients. Geriatr Orthop Surg Rehabil 2022;13:21514593221085813.

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# Integrated approach of data analytics, simulation, and system optimisation to evaluate emergency department performance in Hong Kong: abridged secondary publication

YH Kuo *, JMY Leung, CA Graham, AMC So, HM Meng, KKF Tsoi

## KEY MESSAGES

1. An integrated approach powered by data analytics, simulation, and system optimisation is effective to evaluate solutions to improve emergency department operations.
2. The integrated approach is helpful for hospital administrators and senior management for decision making.
3. The integrated approach can be used not only for emergency department operations but also for other healthcare systems.

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## Introduction

Emergency department (ED) overcrowding is a long-standing issue worldwide.[1,2] This can lead to public safety at risk, prolonged pain and suffering, long waits, and patient dissatisfaction. ED overcrowding blocks timely patient access to emergency care and can be life-ending (causing undue injuries and unnecessary death of emergency patients). We proposed an integrated approach of data analytics, simulation, and system optimisation to evaluate the effect of different policies on ED performance and to provide insights into managing ED operations.

## Methods

Multiple quantitative tools (simulation, data analytics, and system optimisation) were used to identify effective solutions to improve emergency department efficiency. The ED of the Prince of Wales Hospital was studied. Operational data such as triage category, arrival time, start times of triage and consultation, and discharge time of each patient were collected to determine key performance indicators, estimate proportions of patients in different categories, and model the time-varying category-dependent patient arrivals. Service-duration distribution was estimated with end times of triage and consultation.

Based on the patient flow, ED layout, and collected data, simulation model of the ED was developed with the software ARENA (Fig 1). The simulation model captured: all relevant treatment processes (triage, consultation, laboratory tests), intertwining and re-entrant patient-flows, arrival rates that vary by time and patient category, and staff deployment (shift, breaks). Input parameters were patient arrival rates, probability distributions of service durations, available resources, and schedules of doctors and nurses. A large volume of data (eg, time stamps for which patients arrive, start, and end activities, and depart) in various simulated scenarios was generated. Associations between different variables were determined. Optimal solutions were determined by an optimisation approach.

## Results

Patient waiting time prediction, effect of adoption of a fast-track system, workforce planning, and patient scheduling were studied. Both real-time and historical operational data powered by machine learning techniques could achieve personalised and more accurate predictions. Data-driven approaches in combination with the concept of systems thinking can help achieve a better predictive performance.

Four machine learning models (linear regression models, neural networks, support vector machines, and gradient boosting method) and two



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different sets of features were used to predict patient waiting times. Performance of the models was tested through computational experiments.

Set (a) contained 11 features: (1) patient triage categories (three binary variables [urgent, semi-urgent and non-urgent], each indicates if the patient is within the corresponding triage category), (2) arrival time, and (3) numbers of doctors within 3 hours of the patient arrival (seven variables in total: 3, 2, and 1 hour before patient arrival, upon the patient arrival, and 1, 2, and 3 hours after patient arrival.

Set (b) contained 18 features: (1) all features from (a), (2) number of patients in queue for triage upon patient arrival, (3) number of patients in queue for consultation in each category upon patient arrival (five categories in total), and (3) number of patients in queue for departure upon patient arrival.

All models using set (a) features were similar to the baseline model logistic regression(bl) in terms of mean squared error (MSE). Performance of the models significantly improved after deriving the queue lengths from the primary dataset and including them as additional features. Logistic regression(b) could reduce around 15% of MSE from the baseline model. The three machine learning models: neural network(b), support vector machine(b), and gradient boosting(b) outperformed logistic regression(b), with no significant difference in performance among the three. They could reduce around 20% of MSR from logistic regression(bl). Among all models, gradient boosting(b) had the greatest R-squared and the least MSE.

All four machine learning algorithms together with the use of systems knowledge outperformed the baseline model. The stepwise multiple linear regression reduced the MSE by almost 15%. The other three algorithms had similar performances, with reduced MSE by approximately 20%. Reduction of 17% to 22% in MSE after the use of systems knowledge was observed.

We then examined the effect of a fast-track system on enhancing ED performance using a simulation approach. We adopted a similar fast-track system used in the literature,[3-5] in which a fast-track physician is dedicated to the standard and non-urgent (categories 4 and 5) patients, but patients can proceed to regular physicians when the fast-track physician is occupied and regular physicians are free. The rest of the physicians follow the same practice; patients are seen according to their triage category.

Our simulation experiments considered the following scenarios: S0 (simulation model adopting original settings), S1 (20% and 80% of categories 3 and 4 patients, respectively, assuming numbers of categories 1 and 2 patients are negligible), S2 (40% and 60% of categories 3 and 4 patients, respectively, assuming numbers of categories 1 and 2 patients are negligible), S3 (all patient arrival rates decrease by 5%), S4 (all patient arrival rates increase by 5%), S5 (mean consultation time for category 3 patients decreases by 5%), S6 (mean consultation time for category 3 patients increases by 5%), S7 (mean consultation time for category 4 patients decreases by 5%), and S8 (mean consultation time for category 4 patients increases by 5%). In all scenarios, the mean number of patients in the ED and the overall patient waiting time reduced when the fast-track system was adopted (Fig 2).

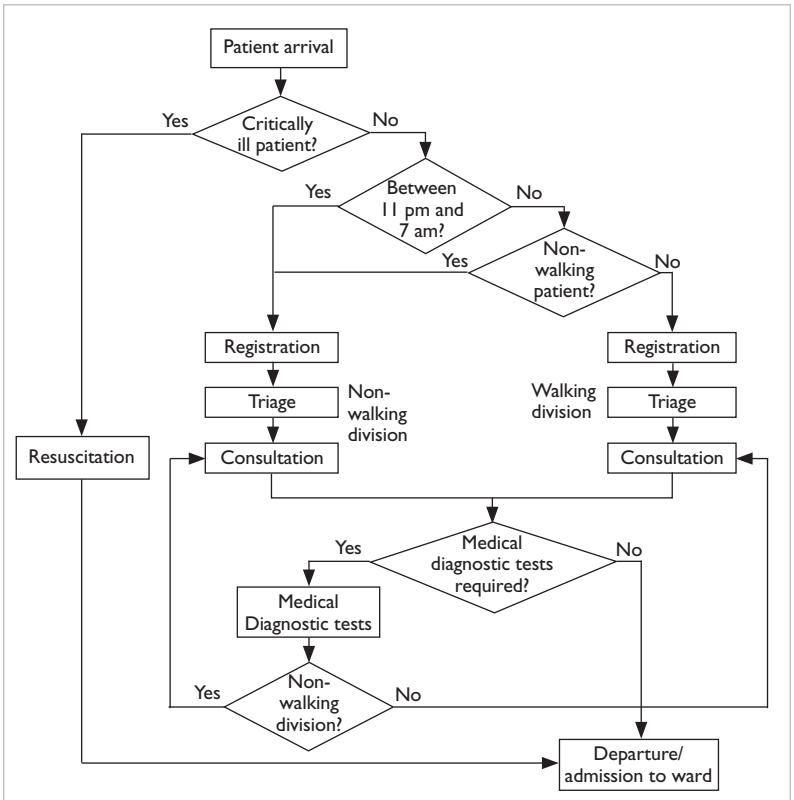


FIG 1. Main logic of simulation model of emergency department patient flow

Several observations were made. The waiting time of category 4 patients was quite sensitive to the number of attendance and the consultation duration. A small change (5%) in the arrival rate or mean consultation time could lead to a big increase in the waiting time of category 4 patients (by comparing S3 to S8 with S0). There was no significant change in doctor utilisation after adoption of the fast-track system under all scenarios. This indicates that the fast-track system did not increase or reduce the physician workloads. Reduction in overall patient waiting time after adoption of the fast-track system was larger when there are more category 3 patients (a reduction of 8.82% in overall patient waiting time in S3, which is the largest among all scenarios), as category 4 patients were expected to wait for a longer time. The fast-track system enabled category 4

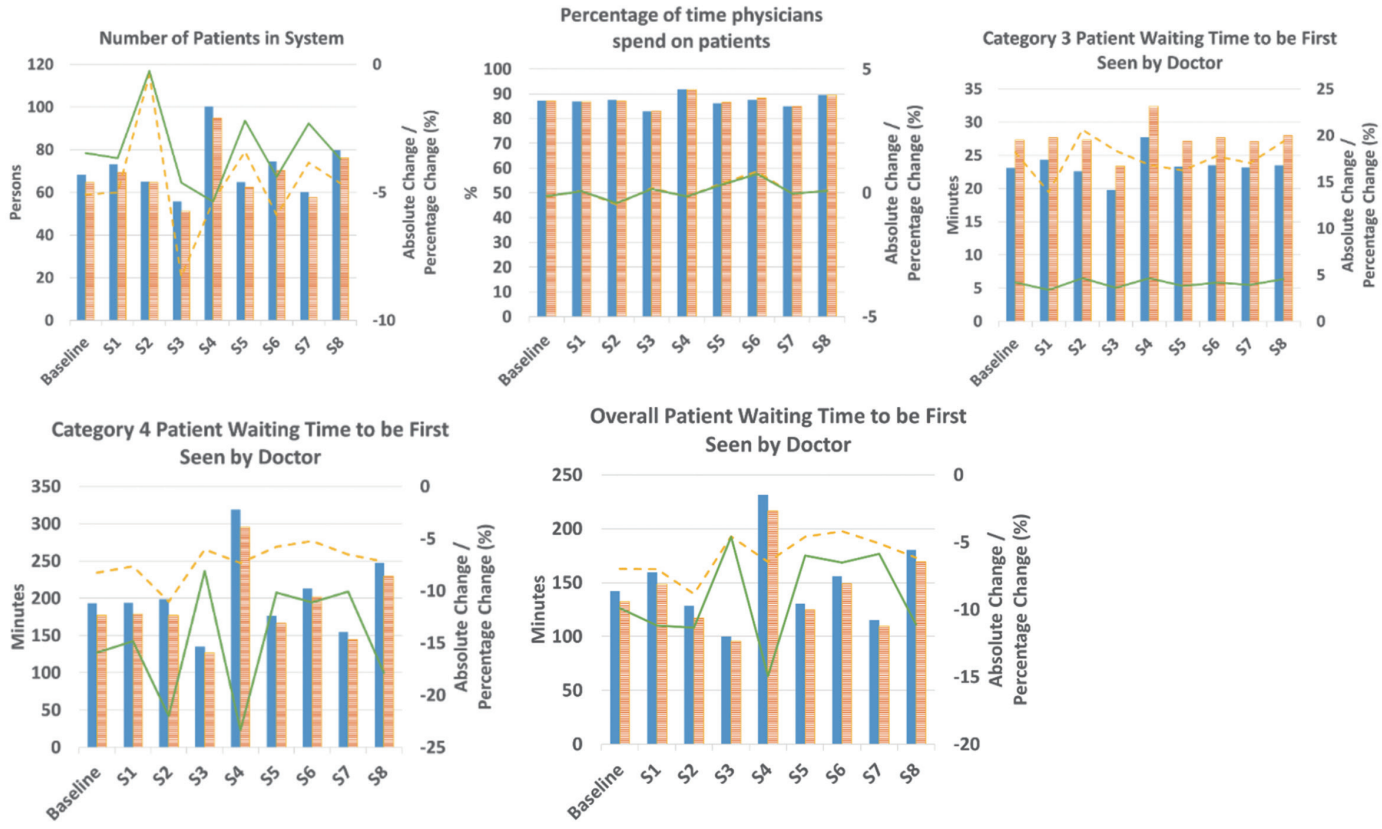


FIG 2. Key performance metrics of emergency department with or without a fast-track physician under difference scenarios

FIG 3. Patterns of patient arrival rate and staffing level

patients to bypass this large group of category 3 patients and therefore reduced their waiting time more significantly. This suggests that the fast-track system is more beneficial to EDs, which have more patients of higher levels of medical urgency.

We propose an optimisation model that optimises the accumulated number of person hours. The optimal staffing level pattern was around 2 hours behind the patient arrival pattern (Fig 3). The insights are that patients typically need to finish other procedures (such as registration and triage) first before consultation with a physician. Physicians can be better utilised when sufficient queue length has been formed.

We propose dynamic scheduling of patients to doctors in ED to minimise weighted tardiness. We propose a greedy heuristic based on priority queues and a general variable neighbourhood search (GVNS). In greedy heuristic, patients are scheduled according to their urgency, whereas in GVNS, the schedule is optimised every time a patient arrived. The GVNS uses six neighbourhood structures and a variable neighbourhood descent to perform the local

search. The GVNS also handles the static problem, solution for which can be used as a reference for the dynamic one. Computational results on 80 instances show that the GVNS better approximated the static problem, in addition to giving an overall reduction of 66.8 percentage points over the greedy heuristic.

## Discussion

An integrated approach powered by data analytics, simulation, and system optimisation is effective to evaluate solutions to improve ED operations. The integrated approach is helpful for hospital administrators and senior management for decision making. The integrated approach can be used not only for ED operations but also for other healthcare systems.

## Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#14151771). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

## Disclosure

The results of this research have been previously published in:

1. Kuo YH, Chan NB, Leung JMY, et al. An integrated approach of machine learning and systems thinking for waiting time prediction in an emergency department. Int J Med Inform 2020;139:104143.
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## Acknowledgements

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# Instant messaging applications to promote smoking cessation in smokers with chronic diseases: abridged secondary publication

**HCW Li *, TH Lam, KY Ho, KWK Lam**

**KEY MESSAGES**

1. Instant messaging applications are a potentially effective option to deliver brief motivational interviewing to help smokers with chronic diseases quit smoking.
2. Delivery of brief motivational interviewing through instant messaging applications is more cost-effective than through face-to-face meetings.
3. The biochemically validated abstinence rate at 12 months is higher (but not significantly) in the intervention than control group (16.7% vs 6.7%, P=0.23).

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## Introduction

Cigarette smoking accounts for 8 million deaths worldwide every year.[1] Smoking may cause development of chronic diseases including cardiovascular disease, chronic respiratory disease, cancer, and diabetes. Smoking is associated with physical inactivity, unhealthy diet, and alcohol consumption.[2,3] Individuals with an intention to improve their health are more likely to engage in desirable health-related lifestyle practices and progress to other healthy practices.[4,5] This study aims to determine the effectiveness of instant messaging applications to deliver brief motivational interviewing (MI) to help smokers with chronic diseases quit smoking.

## Methods

Hong Kong smokers with chronic diseases aged ≥18 years who were followed up in a special out-patient clinic were invited to participate. Those who had no intention to quit smoking (pre-contemplation stage) but were willing to take action to promote health and who were able to use WhatsApp or WeChat and willing to receive health promotion advice were included. Those currently participating in or accessing in other smoking cessation programmes or services were excluded.

Participants were asked about the priority of engaging in any desirable health-related lifestyle practice by a trained nurse (ie, smoking reduction or quitting, regular physical activity, healthy diet, and reduced alcohol consumption). Participants were asked to state a goal that they perceived as the easiest to achieve. Participants were randomly assigned to either the intervention or control group. Those in the control group received a self-help smoking cessation booklet alone, whereas those in the intervention group received an individual face-to-face brief MI (about 5 minutes) with generic health advice on selected health-related lifestyle practice and repeat brief MI messages via WeChat or WhatsApp by the nurse, in addition to a self-help smoking cessation booklet. The brief MI messages were delivered more intensively depending on the participant's responses (usually not less than once per 2 to 3 days and no more than 2 times per day) for the first 6 months.

Participants were assessed at baseline and at 1, 3, 6, and 12 months. The primary outcome measure was biochemically validated 7-day point prevalence of smoking abstinence at 12 months (defined as saliva cotinine level of <115 ng/mL and a carbon monoxide level in expired air of <9 parts per million). Secondary outcome measures were self-reported 7-day point prevalence of smoking abstinence at 6 and 12 months, self-reported reduction of ≥50% in cigarette consumption at 6 and 12 months, and any behavioural change at 6 and 12 months.

## Results

Between 1 June 2019 and 17 July 2020, 82 eligible smokers with chronic diseases attended the special out-patient clinic. Of them, 51 men and 9 women (mean age, 46.2±11.1 years) agreed to participate. Their mean years of smoking and daily cigarette consumption were 25.0±11.0 and 13.5±7.4, respectively. 31 participants had multimorbidity; 54 participants had moderate to severe nicotine dependency; and 52 participants had no previous



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attempts to quit. The intervention (n=30) and control (n=30) groups were comparable at baseline (Table 1).

All participants completed the 1-month follow-up; 42 (70%) participants completed the 3-month follow-up; 50 (83.3%) participants completed the 6-month follow-up; and 43 (71.7%) participants completed the 12-month follow-up.

Biochemical validation was performed for seven participants who self-reported abstinence at 12 months. The intervention group had a higher (but not significantly) biochemically validated abstinence rate at 12 months than the control group (16.7% vs 6.7%, P=0.23, Table 2), with an adjusted odds ratio of 2.4 (P=0.32) after adjusting for age, sex, educational attainment, marital status, employment status, year of smoking, and nicotine dependency. After excluding self-reported quitters, the intervention group had a higher self-reported reduction of ≥50% in daily cigarette consumption at 6 months than the control group (84.6% vs 51.7%, P=0.01), with an adjusted odds ratio of 7.20 (P=0.03). The intervention group had a higher percentage of reported intention to quit at 6 months than the control group (80.1% vs 37.9%, P=0.001) and 12 month (80% vs 50%, P=0.02). More than 80% of participants in the intervention group actively communicated with us via WhatsApp or WeChat.

TABLE 1. Characteristics of participants at baseline

| Characteristic | Intervention (n=30)* | Control (n=30)* | P value |
|---|---|---|---|
| Age, y | 44.3±10.2 | 48.1±12.0 | 0.22 |
| Sex | | | 0.72 |
| Male | 25 (83.3) | 26 (86.7) | |
| Female | 5 (16.7) | 4 (13.3) | |
| Educational attainment | | | 0.94 |
| Primary or below | 4 (13.3) | 5 (16.7) | |
| Secondary | 22 (73.3) | 21 (70.0) | |
| Tertiary | 4 (13.3) | 4 (13.3) | |
| Marital status | | | 0.79 |
| Single | 12 (40.0) | 11 (36.7) | |
| Married | 18 (60.0) | 19 (63.3) | |
| Employment status | | | 0.37 |
| Employed | 24 (80.0) | 21 (70.0) | |
| Unemployed or retired | 6 (20.0) | 9 (30.0) | |
| Diagnosis | | | 0.64 |
| Cardiovascular diseases | 6 (20.0) | 8 (26.7) | |
| Cancer | 1 (3.3) | 0 | |
| Chronic respiratory diseases | 6 (20.0) | 3 (10.0) | |
| Diabetes | 2 (6.7) | 3 (10.0) | |
| Multiple chronic diseases | 15 (50.0) | 16 (53.5) | |
| Duration of smoking, y | 23.1±9.7 | 26.9±12.3 | 0.18 |
| Daily cigarette consumption | 13.5±7.0 | 13.5±7.7 | 0.97 |
| Nicotine dependency | | | 0.54 |
| Mild, 0-3 | 2 (6.7) | 4 (13.3) | |
| Moderate, 4-5 | 10 (33.3) | 7 (23.3) | |
| Severe, 6-10 | 18 (60.0) | 19 (63.3) | |
| Previous quit attempts | | | 1.0 |
| Yes | 4 (13.3) | 4 (13.3) | |
| No | 26 (86.7) | 26 (86.7) | |

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

## Discussion

Smokers with chronic diseases have a long smoking history, relatively high nicotine dependency with no previous attempts at quitting. They are less likely to be affected by the current tobacco-control interventions or policies. In the present study, the biochemically validated abstinence rate at 12 months was higher (but not significantly) in the intervention than control group (16.7% vs 6.7%, P=0.23). The non-significant difference may be attributable to the relatively small sample size. A larger randomised controlled trial is warranted to determine the effectiveness of using instant messaging applications to brief MI to help smokers with chronic diseases quit smoking.

According to the World Health Organization, mobile health is defined as medical and public health practice supported by mobile devices. It is a new strategy to promote health. Instant messaging applications have been increasingly used for health promotion and treatment compliance. Nurses can offer real-time interactions to provide continuous professional advice and personalised support to patients to help them quit smoking and overcome withdrawal symptoms or cravings. Instant messaging applications are more flexible, efficient, and time-saving than face-to-face meetings. A meta-analysis of the use of mobile phone–based interventions for smoking cessation reported that smokers who received instant messages via mobile phones were approximately 1.7 times more likely to abstain from smoking than those who received conventional face-to-face cessation services.

## Funding

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## Disclosure

The results of this research have been previously published in:

TABLE 2. Comparisons of outcomes in the intervention and control groups

| Variable | Intervention group (n=30) | Control group (n=30) | P value | Crude odds ratio (95% confidence interval) | P value | Adjusted odds ratio (95% confidence interval) | P value |
|---|---|---|---|---|---|---|---|
| | No. (%) of participants | | | | | | |
| Biochemically validated 7-day point prevalence of smoking abstinence at 12 months | 5 (16.7) | 2 (6.7) | 0.23 | 3.39 (0.57-20.10) | 0.23 | 2.4 (0.43-13.75) | 0.32 |
| Self-reported 7-day point prevalence of smoking abstinence | | | | | | | |
| At 6 months | 4 (13.3) | 1 (3.3) | 0.35 | 4.46 (0.47-42.51) | 0.19 | 6.23 (0.62-62.94) | 0.12 |
| At 12 months | 5 (16.7) | 2 (6.7) | 0.23 | 3.39 (0.57-20.10) | 0.23 | 2.4 (0.43-13.75) | 0.32 |
| Self-reported reduction of ≥50% in cigarette consumption (excluding self-reported quitters) | | | | | | | |
| 6 months | 22/26 (84.6) | 15/29 (51.7) | 0.01 | 5.13 (1.41-18.66) | 0.01 | 7.20 (1.22-42.44) | 0.03 |
| 12 months | 19/25 (76.0) | 15/28 (53.6) | 0.09 | 2.74 (0.84-8.94) | 0.09 | 3.27 (0.95-11.32) | 0.06 |
| Self-reported behaviour change | | | | | | | |
| 6 months | 12 (40.0) | 9 (30.0) | 0.54 | 1.43 (0.46-4.42) | 0.54 | 1.28 (0.31-5.27) | 0.74 |
| 12 months | 17 (56.7) | 15 (50.0) | 0.61 | 1.31 (0.47-3.62) | 0.61 | 1.09 (0.35-3.40) | 0.88 |

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# Combination of brief advice, nicotine replacement therapy sampling, and active referral for smoking expectant fathers: abridged secondary publication

**MP Wang *, TT Luk, TH Lam, WHC Li, WC Leung, KY Leung, KW Cheung, C Kwa, KH Siong, KK Tang, KW Lee**

## KEY MESSAGES

1. The effectiveness of a combination of brief advice, 1-week nicotine replacement therapy sampling, and active referral for smoking cessation was assessed in 1053 smoking expectant fathers recruited from prenatal clinics of seven public hospitals in Hong Kong.
2. Biochemically validated abstinence was significantly higher in smoking expectant fathers who received a combination of smoking cessation intervention than those who received brief advice alone (6.8% vs 3.6%, P=0.02).
3. Provision of brief smoking cessation intervention to expectant fathers should be a part of routine practice in prenatal care.

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## Introduction

The World Health Organization recommends interventions to help expectant fathers quit smoking to protect mothers and children from second-hand smoke exposure.[1] Nonetheless, only one randomised controlled trial of smoking cessation intervention was identified to target expectant fathers with non-smoking partners.[2] In our previous community-based trial, brief advice with active referral to a smoking cessation service was effective in increasing service uptake and smoking abstinence in smokers.[3] Provision of free sampling of 1 to 2 weeks of nicotine replacement therapy (NRT) is a low-cost intervention for promoting quitting.[4] We aim to evaluate the effect of a combination of brief advice, 1-week NRT sampling, and active referral on smoking cessation in expectant fathers.

## Methods

Daily smoking expectant fathers of their pregnant partners who presented in prenatal clinics of seven public hospitals in Hong Kong were invited to participate. The expectant couples needed to be Hong Kong residents, living together in the past 7 days, and able to communicate in Cantonese or Mandarin. Expectant fathers were daily cigarette smokers whose partners were pregnant and non-smoking in the past 30 days. Those with contraindications to NRT (severe angina, arrhythmia, myocardial infarction), psychiatric diseases or on psychotropic drugs, or who had attended smoking cessation aids or programmes in the past 3 months were excluded.

Participants were randomly assigned in a 1:1 ratio to receive either a combination of brief advice, 1-week NRT sampling, and active referral as guided by the AWARD (ask, warn, advice, refer, do it again) model (intervention) or brief advice to quit on a leaflet by the Department of Health on the hazards of tobacco smoke exposure during pregnancy (control). Pregnant women were not actively intervened; they only received general advice on preventing second-hand smoke exposure.

For the intervention, participants were asked about their smoking behaviours (ask) and then warned about the harms of second-hand smoke



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TABLE 1. Baseline characteristics of participants*

| Characteristics | Intervention (n=527) | Control (n=526) |
|---|---|---|
| Age, y | | |
| 18-25 | 59 (11.3) | 42 (8.1) |
| 26-35 | 272 (51.8) | 280 (53.7) |
| 36-45 | 168 (32.0) | 183 (35.1) |
| 46-55 | 25 (4.8) | 16 (3.0) |
| 56-65 | 1 (0.2) | 0 |
| Education level | | |
| Junior secondary or below | 155 (30.3) | 156 (30.5) |
| Senior secondary | 243 (47.5) | 224 (43.8) |
| Tertiary | 114 (22.3) | 132 (25.8) |
| Daily cigarette consumption | | |
| 1-10 | 365 (69.3) | 362 (68.8) |
| 11-20 | 153 (29.0) | 158 (30.0) |
| ≥21 | 9 (1.7) | 6 (1.1) |
| Time to first cigarette of the day, min | | |
| >60 | 237 (45.0) | 240 (45.6) |
| 31-60 | 77 (14.6) | 76 (14.4) |
| 5-30 | 72 (13.7) | 88 (16.7) |
| <5 | 141 (26.8) | 122 (23.2) |
| Heaviness of smoking | | |
| Light | 355 (67.4) | 370 (70.3) |
| Moderate | 165 (31.3) | 150 (28.5) |
| Heavy | 7 (1.3) | 6 (1.1) |
| Exhaled carbon monoxide level, ppm | 14 (8-23) | 14 (8-22) |
| Past quit attempt | | |
| Never | 206 (39.1) | 198 (37.7) |
| Over 12 months ago | 260 (49.3) | 283 (53.9) |
| Within 12 months | 61 (11.6) | 44 (8.4) |
| Readiness to quit | | |
| Undecided | 403 (76.5) | 397 (75.5) |
| Within 60 days | 21 (4.0) | 19 (3.6) |
| Within 30 days | 47 (8.9) | 50 (9.5) |
| Within 7 days | 56 (10.6) | 60 (11.4) |
| Perception of quitting, 0-10 | | |
| Importance | 9 (7-10) | 8 (7-10) |
| Difficulty | 8 (5-10) | 8 (5-10) |
| Confidence | 5 (5-8) | 5 (5-8) |
| Stage of pregnancy of the pregnant women | | |
| 1st trimester | 108 (21.1) | 105 (20.5) |
| 2nd trimester | 290 (56.8) | 288 (56.3) |
| 3rd trimester | 113 (22.1) | 119 (23.2) |
| Smoking status of pregnant women | | |
| Never | 272 (52.1) | 308 (59.5) |
| Just tried | 73 (14.0) | 62 (12.0) |
| Quit before pregnancy | 48 (9.2) | 45 (8.7) |
| Quit after pregnancy | 129 (24.7) | 103 (19.9) |
| Living with another smoker | | |
| No | 411 (79.5) | 406 (78.7) |
| Yes | 106 (20.5) | 110 (21.3) |

* Data are presented as No. (%) of participants or median (interquartile range), with missing data in some variables

exposure to pregnant women, fetus, and children (warn) using a leaflet. Then, participants were advised to quit smoking as soon as possible (advise) and offered referral to a local smoking cessation service (refer). Researchers used the leaflet to introduce the service and encouraged participants to select a service (counselling and pharmacotherapy). Contacts of those who were willing to be referred were sent to their selected service provider for smoking cessation treatment. Participants received two telephone boosters within a month after baseline assessment by a research nurse. The nurse repeated the AWARD advice during the boosters (do-it-again) and monitored and addressed any issue related to the use of NRT sample. Participants were offered a 1-week sample of NRT patch or gum. The dosing and forms of the NRT were based on the participants' daily cigarette consumption. Those who smoked <10, 10-20 and ≥20 cigarettes per day were offered 2 mg gum, 14 mg patch, and 21 mg patch, respectively. Brief instructions on how to use the NRT products and handle potential adverse effects were provided. Participants could obtain free NRT from smoking cessation services to which they were referred.

Data were collected at baseline using face-to-face questionnaire and at 3 months and 6 months via telephone interview. The primary outcome was biochemically validated tobacco abstinence at 6 months as measured by an exhaled carbon monoxide level of ≤3 parts per million using a Smokerlyzer. Participants who self-reported to have quit smoking for ≥7 days were invited for the test with a small cash incentive of HK$300. Secondary outcomes included self-reported 24-week continuous abstinence at 6 months, 7-day point-prevalence abstinence, 24-hour quit attempt, use of any NRT product, and use of smoking cessation service at 3 and 6 months. Other outcomes in continuing smokers included smoking reduction (defined by at least 50% reduction in cigarette consumption from baseline), change in cigarette dependence (assessed by the Heaviness of Smoking Index), and change in readiness to quit.

The sample size was calculated based on our previous randomised controlled trial of brief advice and active referral,[3] which reported an intervention effect of 1.85 and a validated quit rate of 5.0% in the control group by intention-to-treat analysis. With 80% power and allocation ratio of 1:1, 1148 (574 per group) participants were needed to detect an intervention effect at 2-sided 5% level of significance. Analyses were conducted in Stata/MP version 15.1. Participants with missing outcomes were assumed to have no change in smoking behaviours after baseline. Logistic regressions were used to determine the odds ratio (OR) of the intervention effect on outcomes. Multivariable regressions, multiply-imputed data analyses, and complete case analyses were conducted for the abstinence outcomes.

TABLE 2. Primary and secondary outcomes in the intervention and control groups

| Outcome | Intervention (n=527) | Control (n=526) | Odds ratio (95% confidence interval) | P value |
|---|---|---|---|---|
| | No. (%) of participants | | | |
| Biochemically validated abstinence at 6 months | 36 (6.8) | 19 (3.6) | 1.96 (1.11–3.46) | 0.02 |
| Self-reported 24-week continuous abstinence at 6 months | 38 (7.2) | 21 (4.0) | 1.87 (1.08–3.23) | 0.03 |
| Self-reported 7-day point-prevalence abstinence at 3 months | 91 (17.3) | 65 (12.4) | 1.48 (1.05–2.09) | 0.03 |
| Self-reported 7-day point-prevalence abstinence at 6 months | 139 (26.4) | 90 (17.1) | 1.74 (1.29–2.34) | <0.001 |
| 24-hour quit attempt at 3 months | 213 (40.4) | 171 (32.5) | 1.41 (1.08–1.80) | 0.008 |
| 24-hour quit attempt at 6 months (cumulative) | 314 (59.6) | 259 (49.2) | 1.52 (1.19–1.94) | <0.001 |
| Use of any nicotine replacement therapy product at 3 months | 150 (28.5) | 9 (1.7) | 22.6 (11.4–45.0) | <0.001 |
| Use of any nicotine replacement therapy product at 6 months (cumulative) | 184 (34.9) | 10 (1.9) | 27.7 (14.4–53.1) | <0.001 |
| Use of smoking cessation service at 3 months | 15 (2.8) | 7 (1.3) | 2.17 (0.88–5.37) | 0.09 |
| Use of smoking cessation service at 6 months (cumulative) | 25 (4.7) | 15 (2.9) | 1.70 (0.88–3.26) | 0.11 |

## Results

From 10 October 2018 to 8 February 2020, we approached 11 958 expectant fathers in the prenatal clinics and received 15 online registrations. Of 1415 eligible participants, 1053 (74.4%) consented to participate and were randomised to the intervention (n=527) or control group (n=526). Recruitment was ended early for superiority of the intervention.

Baseline characteristics of the two groups were similar (Table 1). 85.8% of the participants were aged 26 to 45 years; 31.1% had moderate to high heaviness of smoking; 38.4% had never tried to quit; and 79.8% were not ready to quit in 30 days. The smoking profile between participants and eligible smokers who refused to participate were similar (data not shown).

The retention rates were similar between the two groups at 3 months (75.3% vs 76.1%, P=0.79) and at 6 months (81.6% vs 79.8%, P=0.47). Biochemically validated abstinence at 6 months was significantly higher in the intervention than control group (6.8% vs 3.6%, OR=1.96, P=0.02, Table 2), as were self-reported 24-week continuous abstinence at 6 months, self-reported 7-day point-prevalence abstinence, 24-hour quit attempt, and use of any NRT product, but not use smoking cessation service.

In self-reported continuing smokers, intervention resulted in a greater reduction in cigarette dependence at 6 months (-0.37 vs -0.15, P=0.003). The abstinence results were robust, with ORs being 2.04 (1.13-3.67) [P=0.02] after adjusting for baseline characteristics, 2.15 (1.24-3.73) [P=0.007] in multiply-imputed data analysis, and 1.93 (1.09-3.42) [P-0.02] in complete case analysis.

## Discussion

A combination of brief advice, 1-week NRT sample, and referral to a smoking cessation service nearly doubled the odds of validated abstinence in smoking expectant fathers, compared with brief advice alone. The real-world effect might be underestimated because expectant fathers typically do not receive any treatment during prenatal visits, and our control group received brief advice. Our biochemically validated abstinence result (OR=1.96) appeared to be greater than the self-reported abstinence result (OR=1.5) reported in previous trials of NRT sampling in primary care clinics[4] and the validated abstinence result (OR=1.85) after active referral in community-based smokers.[3]

Strengths of the present study included the large sample size (n=1053) in an understudied population (expectant fathers), high retention rate (>80%), and the use of biochemical validation (vs self-reported) abstinence as the primary outcome. The similar smoking profile between participants and eligible subjects who refused to participate indicates the representativeness of our sample to the target population. However, there are some limitations. First, attrition bias could not be excluded despite the high retention rate. The use of intention-to-treat analyses preserved randomisation but underestimated the quit rates. Nevertheless, sensitivity analyses using multiply-imputed and complete data showed that the results were robust to missing data. Second, only a fraction of participants who self-reported quitting participated in the biochemical validation, but the effect sizes of validated and self-reported abstinence were similar. Third, the trial targeted smoking expectant fathers; the generalisability of the findings to other populations were uncertain.

In Hong Kong, about 29% of mothers with a newborn reported that their partners were smokers.[5]

Pregnancy presents an opportune time to engage expectant fathers in smoking cessation to protect their partners and children and themselves. Our findings support provision of brief cessation interventions to all expectant fathers visiting prenatal clinics. Further research is warranted to translate the results into practice and test the intervention in other settings to increase the reach of effective smoking cessation treatment.

## Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#15162691). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

## Disclosure

The results of this research have been previously published in:

1. Luk TT, Lam TH, Leung WC, et al. Brief advice, nicotine replacement therapy sampling, and active referral for expectant fathers who smoked cigarettes: a randomized clinical trial. JAMA Intern Med 2021;181:1081-9.
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# Chinese version Weight-Related Eating Questionnaire to assess psychological aspects of eating behaviours in Chinese adults: abridged secondary publication

M Ho *, R Smith, PH Chau, CY Chung, DYT Fong

KEY MESSAGES

1. The 13-item Chinese version Weight-Related Eating Questionnaire has good reliability and validity to assess Chinese adults' psychological aspects of eating behaviour including routine restraint, compensatory restraint, susceptibility to external cues, and emotional eating.
2. This instrument can be used to identify the underlying psychological aspects of eating behaviour associated with overeating and obesity so that effective educational and environmental strategies can be designed to reduce the obesity epidemic.

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## Introduction

The psychological aspects of eating behaviour include susceptibility to external cues, emotional eating, and dietary restraint (or restrained eating). All are likely to be associated with overeating and high energy intake and hence obesity.[1,2] The most widely used tools to assess the psychological aspects of eating behaviour are the 51-item Three-Factor Eating Questionnaire (TFEQ) and the 33-item Dutch Eating Behaviour Questionnaire (DEBQ). However, the length of these questionnaires is a limitation to their usage.

The 16-item Weight-Related Eating Questionnaire (WREQ) combines the strengths of both the TFEQ and DEBQ.[3] It assesses susceptibility to external cues and emotional eating, routine restraint and compensatory restraint. It has good construct validity and criterion-related validity.[3,4] This study aims to translate the WREQ into Chinese and then validate the Chinese version in Hong Kong Chinese adults.

## Methods

In stage 1, linguistic validation was conducted according to the World Health Organization guideline on the process of translation and adaptation. The WREQ was forward-translated to Chinese and then backward-translated to English. Content validity was assessed by an expert panel consisting of a doctor, a nurse, a psychologist, a public health nutritionist, and two dietitians who work in the obesity field. Six new items (three for emotional eating subscale and three for susceptibility to external cues subscale) were added to the Chinese version WREQ (WREQ-C). The 22-item WREQ-C was pilot-tested in 18 Chinese adults. It consists of four constructs of eating behaviours: routine restraint (3 items), compensatory restraint (3 items), susceptibility to external cues (8 items), and emotional eating (8 items). Each item is measured with a 5-point Likert scale: 1 (not at all), 2 (sometimes), 3 (half of the time), 4 (most of the time), and 5 (always).

In stage 2, a convenience sample of 1007 Chinese adults aged ≥18 years from the community were invited to complete an online survey. Those with a self-reported health condition that requires special dietary restriction or a self-reported history of eating disorder diagnosis were excluded.

Psychometric properties of the WREQ-C were first evaluated based on the item response theory (IRT). Polytomous generalised partial credit item IRT models were used to evaluate items within each subscale. Separate models were conducted for each subscale. Item and subscale were evaluated using three criteria: (1) test information area of the subscale to be maintained within 80% of the original structure of the WREQ, (2) subscale retains a convergent construct validity to the relevant DEBQ using hypothesis testing, and (3) internal consistency of the subscale to be maintained ($\alpha \geq 0.7$). Item reduction was conducted when subscales achieved all three criteria, and the item with the lowest discriminative value was removed until the new structure of the subscale failed in one of these criteria.

The reduced scale was then examined for content validity, structural validity, internal



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consistency, test-retest reliability, and convergent validity. Structural validity was assessed using a confirmatory factor analysis. A four-factor model was fitted using weighted least square mean and variance-adjusted estimators and categorical variables and was tested using model fit statistics (Chi-square, comparative fit index, Tucker-Lewis index, weighted root mean square residual, and root mean square error of approximation). A priori hypothesis testing was used to evaluate the convergent validity of the WREQ-C using the Chinese version DEBQ as a reference.

## Results

The 1007 participants were aged 18 to 71 years; 68% were single; and 78% had a bachelor's degree or above (Table).

In item response theory analyses, a three-item structure was retained for the routine restraint subscale, with a test information area of 17.5. The subscale correlated with the DEBQ restrained eating subscale ($r$=0.71, P<0.001), with internal consistency of α=0.76. Item 3 showed the lowest discriminative value, but internal consistency dropped below the criteria threshold (α=0.66) when item 3 was removed. Test information curves for the routine restraint subscale displayed items providing more information at higher levels (θ=0) of the latent trait (Fig 1a).

The three-item structure was retained for the compensatory restraint subscale, with a test information area of 32.5. The subscale correlated with the DEBQ restrained eating subscale ($r$=0.61, P<0.001), with internal consistency of α=0.78. Test information area dropped to <80% of the original when an additional item was removed (test information area of two items was 22.4, which was 69% of the original). Test information curves for the compensatory restraint subscale displayed items providing more information at three separate levels of the latent trait (Fig 1b).

The original susceptibility to external cues subscale had a test information area of 23.4. After adding the three new items (item 20, 21 and 22) and then removing the lowest discriminative value until the criteria could not be maintained, a three-item structure (items 8, 9, and 13) was resulted, with a test information area of 21.7 (93% of the original). Removing any further item resulted in the test information area below 80% of the original structure. The three-item structure of the susceptibility to external cues subscale correlated with the susceptibility to external cues subscale of the DEBQ ($r$=0.62, P<0.001), with internal consistency of α=0.72. Test information curves for the new structure of the susceptibility to external cues subscale displayed items providing more information at higher ability of the average level (θ=0) of the latent trait (Fig 1c).

TABLE. Characteristics of participants (n=1007)

| Characteristic | Value* |
|---|---|
| Female sex | 739 (73) |
| Age, y | 32.6±13.7 |
| ≤29 | 562 (56) |
| ≥30 | 445 (44) |
| Body mass index, kg/m$^2$ (n=949) | 21.3±3.0 |
| Underweight | 139 (15) |
| Normal weight | 508 (54) |
| Overweight | 136 (14) |
| Obese | 166 (17) |
| Self-reported health status | |
| Extremely well | 24 (2) |
| Very well | 240 (24) |
| Well | 361 (36) |
| Fair | 351 (35) |
| Bad | 31 (3) |
| Marital status (n=1006) | |
| Single | 684 (68) |
| Married | 294 (29) |
| Divorced/separated/widowed | 28 (3) |
| Employment status | |
| Full-time | 481 (48) |
| Part-time | 37 (4) |
| Retired/unemployed/homemaker | 78 (8) |
| Student | 411 (41) |
| Education level (n=1006) | |
| Senior secondary or below | 118 (12) |
| Diploma/certificate/associate degree | 104 (10) |
| Bachelor degree | 510 (51) |
| Master degree or above | 274 (27) |
| Family monthly income, HK$ (n=1000) | |
| <9999 | 110 (11) |
| 10 000-19 999 | 178 (18) |
| 20 000-29 999 | 196 (20) |
| 30 000-39 999 | 154 (15) |
| 40 000-59 999 | 170 (17) |
| ≥60 000 | 192 (19) |
| Subscale score | |
| Routine restraint (1-5) | 2.0±0.9 |
| Compensatory restraint (1-5) | 2.8±1.0 |
| External eating (1-5) | 2.5±0.8 |
| Emotional eating (1-5) | 2.1±0.9 |

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

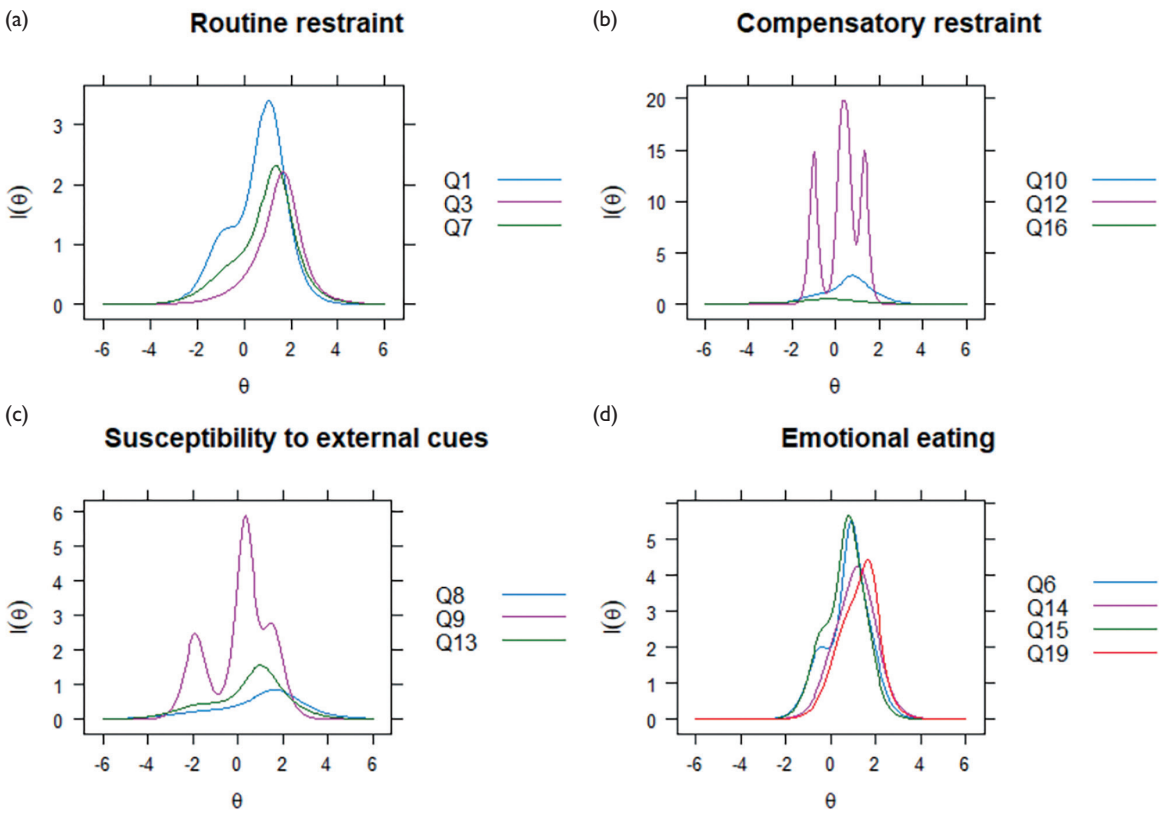


FIG 1. Test information curves of the (a) routine restraint subscale, (b) compensatory restraint subscale, (c) susceptibility to external cues subscale, and (d) emotional eating subscale of the Chinese version Weight-Related Eating Questionnaire. Latent trait (θ) is shown on the horizontal axis, and the amount of information (I(θ)) is shown on the vertical axis

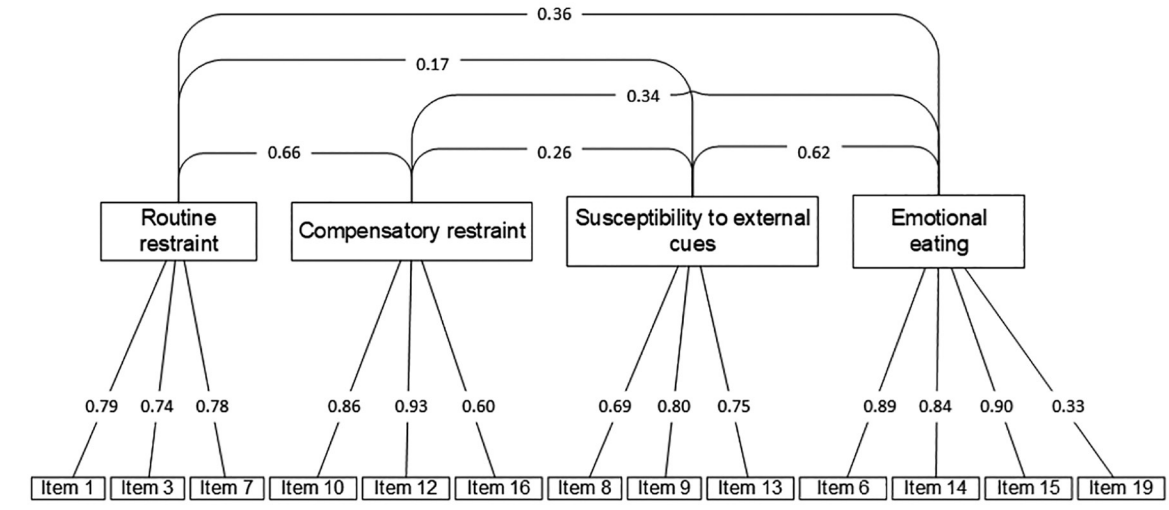


FIG 2. Confirmatory factor analysis of the four-factor 13-item Chinese version Weight-Related Eating Questionnaire

The original structure of the emotional eating subscale had a test information area of 48.5. Three new items (items 17, 18, and 19) were added. After item reduction, a 4-item structure (items 6, 14, 15, and 19) was resulted, with a test information area of 40.5 (83% of the original structure). Removing any further items resulted in the test information area below 80% of the original structure. The 4-item structure of the emotional eating subscale correlated with the diffuse emotion subscale ($r$=0.73, P<0.001),

labelled emotion subscale ($r$=0.79, P<0.001), and emotional eating subscale ($r$=0.81, P<0.001) of the DEBQ, with internal consistency of α=0.89. Test information curves for the 4-item emotional eating subscale displayed items providing more information at higher ability of the average level (θ=0) of the latent trait (Fig 1d). The IRT analysis resulted in a 13-item WREQ-C structure.

In confirmatory factor analysis of the 13-item WREQ-C, a four-factor model displayed acceptable fit to the data; correlations between items and their designated factors were strong (standardised β>0.6), with an exception of item 19 (Fig 2). Goodness of fit was acceptable in terms of comparative fit index (0.97), Tucker-Lewis index (0.97), and root mean square error of approximation (0.06, P<0.001), but weighted root mean square residual was 1.22, which did not meet the predetermined model fit criteria, with Chi-square being 277.45 (degree of freedom=59, P<0.001).

A sub-sample of 31 participants (61% females) aged 18 to 65 years with different weight status and education levels were asked to complete the questionnaire for a second time after a 2-week interval. The intraclass correlation coefficients (95% confidence interval) for all subscales were high: 0.76 (0.55-0.87) for routine restraint, 0.76 (0.55-0.87) for compensatory restraint, 0.78 (0.57-0.91) for susceptibility for external cues, and 0.89 (0.77-0.97) for emotional eating (all P<0.001).

## Discussion

Validity and reliability of the 13-item WREQ-C were maintained, compared with the original English version.[3] Culture has a strong influence on eating behaviour. Six new items (items 17 to 22) were added by the expert panel, but only item 19 (I eat more when I am having relational problems with my family) provided additional information and was retained. This reflects the role of family relationship on emotional eating in Chinese adults.

The four-factor 13-item WREQ-C demonstrated satisfactory convergent validity with the corresponding subscales of DEBQ ($r$=0.61-0.81), good internal consistency (α=0.72-0.81), and good test-retest reliability (intraclass correlation coefficient of >0.7 for all subscales). The WREQ-C is a reliable instrument to assess Hong Kong adults with various weight status and age groups. The structural validity was good in terms of comparative fit index (>0.90), Tucker-Lewis index (>0.90), and root mean square error of approximation (0.06).

China had the second largest number of obese adults worldwide in 2015, following the United States.[5] As the psychological aspects of eating behaviours including susceptibility to external cues, emotional eating, and restraint eating may be associated with overeating and high energy intake and hence obesity, a reliable and valid instrument to assess these specific eating behaviours is critical in obesity research and clinical practice. The 13-item WREQ-C is a relatively brief, compared with DEBQ and TFBQ. A brief instrument may reduce the response burden and increase completion rates.

One limitation to the present study is the convenience sampling, which may limit the generalisability of the findings to other populations. However, the large sample size of participants with various body weight statuses and ages allows a comprehensive evaluation of the psychometric properties of the WREQ-C.

## Conclusions

The 13-item WREQ-C has good reliability and validity to assess Chinese adults' psychological aspects of eating behaviours including routine restraint, compensatory restraint, susceptibility to external cues, and emotional eating. It can be used to identify underlying psychological aspects of eating behaviours associated with overeating and obesity so that more effective educational and environmental strategies can be designed to reduce the obesity epidemic.

## Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#16172861). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

## Disclosure

The results of this research have been previously published in:

1. Ho M, Smith R, Chau PH, Chung CY, Schembre SM, Fong DYT. Psychometric evaluation of the Chinese version of a Weight-Related Eating Questionnaire using an item response theory approach. Nutrients 2022;14:1627.

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# Electro-acupuncture for central obesity: abridged secondary publication

**LLD Zhong *, S Zhang, E Wong, C Cao, ZX Bian**

**KEY MESSAGES**

1. A total of 168 participants with central obesity were randomly assigned to the electro-acupuncture group (n=84) or the sham group (n=84). 91.7% and 90.5% of participants in the respective groups completed all treatment sessions and follow-ups.
2. Electro-acupuncture was found to have greater benefits on waist circumference, body weight, BMI, hip circumference, waist-to-hip circumference ratio, and body fat percentage than sham acupuncture.
3. Results of this study provide evidence for the safety and effectiveness of electro-acupuncture for treatment of central obesity.

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## Introduction

Central obesity is strongly associated with insulin resistance, dyslipidaemia, and systemic inflammation and plays a crucial role in the pathogenesis of certain chronic diseases.[1-3] Acupuncture can adjust various metabolic functions, improve fat decomposition, reduce blood triglycerides levels, and thus achieve weight loss. The effectiveness and safety of electro-acupuncture have been reported.[4,5] We previously reported that a combination of electro-acupuncture and auricular acupressure could significantly reduce the body weight and body mass index (BMI), compared with sham control. However, objective metabolic parameters were not tested. Waist circumference is an indicator of body fat distribution and central obesity. This study aims to evaluate the effect of electro-acupuncture on central obesity.

## Methods

Participants aged 18 to 65 years who had central obesity, waist circumference of ≥90 cm (for men) and ≥80 cm (for women), and BMI of ≥25 kg/m$^2$ were recruited through advertisement. They had not received weight-loss treatment in the past 3 months. Those with endocrine system diseases (thyroid disorder, pituitary disorder, and sex gland disorder), impaired hepatic or renal function, heart disease (arrhythmia, heart failure, myocardial infarction, and having a pacemaker), pregnant or lactating women, bleeding tendency, allergy and immunology disease, bleeding coagulation disorders, stroke or otherwise unable to exercise were excluded.

Participants were randomly assigned to receive 16 sessions (twice a week for 8 weeks) of electro-acupuncture or sham acupuncture by registered traditional Chinese medicine practitioners with at least 3 years of clinical experience. Participants were followed up at 4 weeks, 8 weeks, and 16 weeks after completion of treatment.

The acupoints used were Zusanli (ST-36), Sanyinjiao (SP-6), Tianshu (ST-25), Fenglong (ST-40), Zhongwan (CV-12), Qihai (CV-6), Daheng (SP-15), and Daimai (GB-26). The needle retention time was 30 minutes. Participants were instructed to lie supine on a bed, exposing the abdomen and legs for disinfection. Acupuncture needles (verum acupuncture needles Asia-med Special No. 16 with 0.30 × 0.30 mm matching the Streitberger sham-needles) were used for 14 acupoints. The insertion depth was about 10 to 25 mm to achieve Deqi sensation (a feeling of soreness, numbness, heaviness, and pressure soreness by the patient or a feeling of heavy, tight, astringent, stagnant by the practitioner). Electro-acupuncture was then applied to the abdominal points with 50 Hz densely dispersed waves at 50 volts through an electric needle stimulator (ES-160 6-Channel Programmable Electro-acupuncture), and the handle of the needle started to tremble slightly.

For sham control, Streitberger's non-invasive acupuncture needle (specification 8 x 1.2 inches / 0.30 × 30 mm) was used at the same acupoints in the same stimulation manner, but the needles only adhered to the skin. The sham acupuncture also was connected to an electric needle stimulator but no electrical stimulation to the body. The stimulator emitted the same beeping sound and flashing light continuously.

All participants received unilateral auricular acupressure at four auricular points: Hunger, Shen men, Spleen, and Stomach, with Semen Vaccariae



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(Wang Bu Liu Xing) embedded within adhesive tape in each treatment session. We did not apply sham acupressure to avoid reducing the pure acupuncture effects. Participants were instructed to repeatedly press the tape with fingertips for 1 minute per point, thrice per day. The embedded tape was retained in situ for 24 hours, and then the alternate ear was treated at the next visit.

All participants were advised to take a regular number of meals daily and not intake any snacks. Meals comprised one bowl of rice (210 g) for participants >70 kg and two-thirds of a bowl of rice (140 g) for those <70 kg, with instructions to eat side dishes balanced with the rice. In addition, participants were required not to take exercise, except for essential activities in daily work.

The primary outcome was the change in waist circumference. The secondary outcomes included the changes in hip circumference, waist-to-hip circumference ratio, BMI, body fat percentage, and body weight. Participants were evaluated at the first, fourth, eighth, and sixteenth sessions of treatment and at the follow-up.

## Results

A total of 168 participants were randomly assigned to receive electro-acupuncture (n=84) or sham acupuncture (n=84). 91.7% and 90.5% of participants in the respective groups completed all treatment sessions and follow-ups. The baseline characteristics of the two groups were comparable at baseline.

At 8 weeks after treatment, decreases in the waist circumference, body weight, BMI, hip circumference, waist-to-hip circumference ratio, and body fat percentage were significantly greater in the electro-acupuncture group than in the sham acupuncture group. There were no serious adverse events in both groups.

## Discussion

Electro-acupuncture was found to have greater benefits on waist circumference, body weight, BMI, hip circumference, waist-to-hip circumference ratio, and body fat percentage than sham acupuncture. Results of this study provide evidence for the safety and effectiveness of electro-acupuncture for treatment of central obesity.

## Conclusion

Our findings provide evidence of efficacy and safety of electro-acupuncture and auricular acupressure for treating central obesity.

## Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#15163331). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

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# Self-administered acupressure for insomnia: abridged secondary publication

**WF Yeung *, KF Chung, ZJ Zhang, LX Lao, LKP Suen, FYY Ho, LM Ho**

**KEY MESSAGES**

1. Self-administered acupressure results in significantly greater reduction in symptom severity of insomnia at weeks 4 and 8, compared with sleep hygiene education.
2. Self-administered acupressure results in greater improvement in anxiety, depression, and health-related quality of life at week 8, compared with sleep hygiene education.
3. A short training course (two 2-hour sessions) of self-administered acupressure is an acceptable first-step intervention for people with insomnia.

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## Introduction

Insomnia is a prevalent sleep disorder. Early diagnosis and treatment of insomnia are crucial, because the condition may lead to anxiety and depressive disorders if left untreated. Pharmacotherapies such as benzodiazepines and non-benzodiazepine hypnotics are effective but are associated with abuse, dependence, and uncertain efficacy with long-term use. Psychological and behavioural therapies are also effective but remain underused in primary care possibly owing to the need for advanced training for effective implementation.

Acupressure is a non-invasive variant of acupuncture and can be self-administered after proper training. It has positive effects on improving sleep quality on cancer patients, menopausal women, and hypertensive patients.[1] It also has greater effects on older people with poor sleep quality than sleep hygiene education has.[2] However, the effectiveness of self-administered acupressure against insomnia remains unknown, owing to the lack of the use of standardised sleep assessments (sleep diary and actigraphy) and unclear diagnostic method of insomnia.[1] We therefore conducted a randomised controlled trial to determine the effects of self-administered acupressure for insomnia in general adults using standard sleep outcome measures.

## Methods

This study was conducted from October 2018 to September 2020. Participants were randomly assigned to receive two 2-hour sessions, 1 week apart, of either self-administered acupressure or sleep hygiene education in a 1:1 ratio. Participants were instructed to perform self-administered acupressure or sleep hygiene every night and record their practice in a logbook. Participants were assessed at baseline, week 4, and week 8 by a research assistant blind to the group allocation. The primary outcome was the severity of insomnia symptoms and related daytime impairment measured by the 7-item self-rated Insomnia Severity Index (ISI). Other measures included subjective sleep parameters by a standardised 7-day sleep diary, objective sleep parameters collected by 7-day wrist actigraphy, mood symptoms by the Hospital Anxiety and Depression Scale (HADS), health-related quality of life by Short-Form Six-Dimension (SF-6D), and credibility and acceptability of treatment by the Credibility of Treatment Rating Scale.

## Results

A total of 200 participants were equally randomised to self-administered acupressure (n=100) or sleep hygiene education (n=100) [Table 1]. The two groups were comparable in terms of participant characteristics, except that the sleep hygiene education group had higher score in ISI (P=0.009) and HADS depression subscale (P=0.04) and lower score in SF-6D (P=0.02).

Both groups had 97 participants completed the first and second lessons. All participants in the



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TABLE 1. Clinical characteristics of participants*

| Variable | All (n=200) | Self-administered acupressure (n=100) | Sleep hygiene education (n=100) |
|---|---|---|---|
| Age, y | 48.0±12.8 | 47.6±12.7 | 48.5±12.9 |
| Female | 150 (75.0) | 74 (74.0) | 76 (76.0) |
| Body mass index, kg/m$^2$ | 22.3±3.5 | 22.4±3.5 | 22.3±3.6 |
| Marital status | | | |
| Single | 59 (29.5) | 31 (31.0) | 28 (28.0) |
| Cohabiting/married | 123 (61.5) | 60 (60.0) | 63 (63.0) |
| Widowed/divorced | 18 (9.0) | 9 (9.0) | 9 (9.0) |
| Education level | | | |
| Secondary education or below | 82 (41.0) | 35 (35.0) | 47 (47.0) |
| Tertiary education | 118 (59.0) | 65 (65.0) | 53 (53.0) |
| Occupation | | | |
| Employed | 102 (51.0) | 54 (54.0) | 48 (48.0) |
| Economically inactive | 80 (40.0) | 34 (34.0) | 46 (46.0) |
| Unemployed | 4 (2.0) | 4 (4.0) | 0 (0.0) |
| Self-employed | 14 (7.0) | 8 (8.0) | 6 (6.0) |
| Insomnia duration, y | 6.1±7.7 | 5.4±7.1 | 6.8±8.1 |
| With chronic disease | 41 (20.5) | 22 (22.0) | 19 (19.0) |
| History of psychiatric comorbidities | 12 (6.0) | 4 (4.0) | 8 (8.0) |

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

self-administered acupressure group passed the fidelity check of the acupressure techniques at the end of training. 92.3% and 88.8% participants in self-administered acupressure group practiced at least 5 days per week during weeks 1 to 4 and during weeks 5 to 8, respectively.

Compared with the sleep hygiene education group, the self-administered acupressure group showed better improvement in ISI score with moderate effect size at weeks 4 and 8 (Cohen's *d*=0.51 and 0.67, respectively, all P<0.001, Table 2), higher proportion of participants with ISI score <10 at week 8 (41.9% vs 11.6%, P<0.001), higher sleep-diary-derived total sleep time and sleep efficiency at week 4 (Cohen's *d*=0.32 and 0.30, respectively, all P=0.03) but not at week 8, greater improvement in HADS anxiety score (Cohen's *d*=0.35, P=0.02) and depression score (Cohen's *d*=0.28, P=0.049) and SF-6D (Cohen's *d*=0.32, P=0.02) at week 8 but not at week 4. However, no significant difference was found between groups in objective sleep parameters by wrist actigraphy (sleep onset latency, wake time after sleep onset, total sleep time, and sleep efficiency) at week 4 or 8.

## Discussion

Self-administered acupressure was more effective than sleep hygiene education in improving insomnia. Participants in the self-administered acupressure group showed longer sleep-diary-derived total sleep time and sleep efficiency at week 4 as well as greater improvement in depression, anxiety, and quality of life at week 8. However, the magnitude of the effect did not reach clinical significance. Self-administered acupressure achieved a moderate effect size in improvement of ISI score (Cohen's *d*=0.51-0.67). In contrast, one study reported a large effect size (Cohen's *d*=1.54) on improving the sleep questionnaire score among older adults with poor sleep.[2] Such difference may be attributed to the longer treatment duration (12 months), higher treatment intensity (30 minutes, twice per day), and additional home visits of the study.[2] Further studies are warranted to determine the optimal dose for self-administered acupressure.

The improvements in total sleep time and sleep efficiency by subjective sleep diary were not confirmed by objective actigraphy. People with insomnia commonly have subjective-objective sleep discrepancy, which is the time difference between self-reported and objectively measured sleep features. Actigraphy is less reliable for differentiating between quiet wakefulness and sleep and tends to overestimate sleep in people with insomnia by including the time lying and waiting to fall asleep and after waking from sleep. Thus, the use of both subjective and objective measurements is

TABLE 2. Insomnia Severity Index and subjective and objective sleep parameters of the two groups at baseline and week 4 and week 8

| Outcomes | Self-administered acupressure (n=100)* | | Sleep hygiene education (n=100)* | | P value | Effect size, Cohen's *d* (95% confidence interval) |
|---|---|---|---|---|---|---|
| | | Change from baseline | | Change from baseline | | |
| Insomnia Severity Index | | | | | | |
| Baseline | 16.00 (0.37) | - | 17.38 (0.45) | - | | |
| Week 4 | 11.32 (0.37) | -4.68 (0.34) | 14.59 (0.45) | -2.79 (0.40) | <0.001 | 0.51 (0.22 to 0.79) |
| Week 8 | 10.41 (0.38) | -5.59 (0.41) | 14.68 (0.46) | -2.70 (0.46) | <0.001 | 0.67 (0.38 to 0.95) |
| Sleep diary | | | | | | |
| Sleep onset latency, min | | | | | | |
| Baseline | 44.06 (3.19) | - | 48.49 (3.69) | - | | |
| Week 4 | 31.84 (3.31) | -12.23 (3.20) | 39.54 (3.78) | -8.95 (3.24) | 0.47 | 0.10 (-0.18 to 0.38) |
| Week 8 | 34.05 (3.34) | -10.01 (3.11) | 35.62 (3.83) | -12.87 (3.52) | 0.55 | -0.09 (-0.36 to 0.19) |
| Wake after sleep onset, min | | | | | | |
| Baseline | 42.84 (2.74) | - | 45.43 (3.85) | - | | |
| Week 4 | 29.91 (2.84) | -12.93 (2.76) | 34.36 (3.93) | -11.07 (3.00) | 0.67 | 0.06 (-0.21 to 0.34) |
| Week 8 | 22.56 (2.90) | -20.28 (3.29) | 33.78 (3.98) | -11.65 (3.39) | 0.08 | 0.26 (-0.02 to 0.54) |
| Total sleep time, min | | | | | | |
| Baseline | 332.41 (6.39) | - | 327.19 (7.40) | - | | |
| Week 4 | 366.43 (6.57) | 34.02 (5.28) | 344.22 (7.55) | 17.03 (5.41) | 0.03 | 0.32 (0.04 to 0.60) |
| Week 8 | 369.60 (6.65) | 37.19 (5.68) | 353.12 (7.13) | 25.93 (5.63) | 0.16 | 0.20 (-0.08 to 0.48) |
| Sleep efficiency, % | | | | | | |
| Baseline | 73.32 (1.26) | - | 71.66 (1.57) | - | | |
| Week 4 | 79.93 (1.29) | 6.61 (1.11) | 75.14 (1.60) | 3.48 (0.99) | 0.03 | 0.30 (0.02 to 0.58) |
| Week 8 | 80.27 (1.31) | 6.95 (1.11) | 77.32 (1.61) | 5.67 (1.16) | 0.42 | 0.11 (-0.16 to 0.39) |
| Actigraphy | | | | | | |
| Sleep onset latency, min | | | | | | |
| Baseline | 20.79 (1.64) | - | 19.66 (1.51) | - | | |
| Week 4 | 20.08 (1.79) | -0.71 (1.80) | 18.03 (1.62) | -1.63 (1.45) | 0.68 | -0.06 (-0.33 to 0.22) |
| Week 8 | 18.37 (1.84) | -2.42 (1.90) | 19.66 (1.51) | -0.69 (1.46) | 0.50 | 0.10 (-0.18 to 0.38) |
| Wake after sleep onset, min | | | | | | |
| Baseline | 32.96 (2.02) | - | 35.10 (2.56) | - | | |
| Week 4 | 30.72 (2.20) | -2.24 (2.13) | 34.34 (2.67) | 0.76 (1.87) | 0.59 | 0.07 (-0.20 to 0.35) |
| Week 8 | 31.64 (2.23) | -1.32 (2.09) | 38.25 (2.78) | 3.15 (2.26) | 0.15 | 0.21 (-0.07 to 0.48) |
| Total sleep time, min | | | | | | |
| Baseline | 394.69 (5.22) | - | 395.25 (5.35) | - | | |
| Week 4 | 401.19 (5.52) | 6.50 (4.26) | 397.69 (5.72) | 2.44 (5.05) | 0.55 | 0.09 (-0.19 to 0.36) |
| Week 8 | 398.00 (5.60) | 3.31 (4.37) | 391.69 (6.00) | -3.56 (5.76) | 0.34 | 0.13 (-0.14 to 0.41) |
| Sleep efficiency, % | | | | | | |
| Baseline | 85.45 (0.68) | - | 85.18 (0.72) | - | | |
| Week 4 | 86.30 (0.73) | 0.84 (0.61) | 85.95 (0.76) | 0.77 (0.59) | 0.93 | 0.01 (-0.27 to 0.29) |
| Week 8 | 86.56 (0.75) | 1.11 (0.68) | 84.89 (0.79) | -0.29 (0.71) | 0.16 | 0.20 (-0.08 to 0.48) |

* Data are presented as mean (standard error), unless otherwise specified

recommended in sleep research. Subjective measure remains the priority, as insomnia is a subjective complaint.

The effects of acupressure on sleep may involve the activation of the parasympathetic nervous system, increase in autonomous responses, and reduction of psychological stress.[1] A functional magnetic resonance imaging study of healthy subjects reported that needling at CV12 could modulate the limbic-prefrontal functional network, which is overlapped with the functional circuits associated with emotional and cognitive regulation.[4] Acupuncture needling at Neiguan (PC6) can reduce heart rate and systolic blood pressure, suggesting its sympatho-inhibitory effect.[5] Whether acupressure on these acupoints would produce the same effects as acupuncture warrants further investigation. Sleep hygiene education is commonly used to control the non-specific effect of practitioner-patient interactions in the randomised controlled trials of self-help and psychological interventions for insomnia.

The present study has limitations. Polysomnographic screening was not used although patients with other sleep disorders such as sleep apnoea and narcolepsy were excluded. In addition, participants were predominantly female (75%) and relatively well educated (>50% having tertiary education). This may limit the generalisability of the findings. The sleep hygiene education group had a significantly higher ISI score (more severe insomnia) at baseline, which may inflate the effect size. Although sleep hygiene education may be used to control the practitioner-patient interactions and contact time, specific components such as precise acupoint stimulation were not examined. Further research may include a sham control.

## Conclusion

Self-administered acupressure taught in a short training course is effective to improve sleep and related daytime impairment and mood problems in people with insomnia in short term (up to week 8). Self-administered acupressure is easy to learn, non-invasive, and less time-intensive; it is an acceptable first-step care for insomnia.

## Funding

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## Disclosure

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# Effect of berberine on cardiovascular disease risk factors: abridged secondary publication

J Zhao *, DKM Ip, JYY Leung, D Vackova, X He, CM Schooling

KEY MESSAGES

1. In Chinese men, berberine lowers total cholesterol and probably lowers low-density lipoprotein cholesterol, with good safety and tolerability.
2. Berberine does not lower testosterone in men, which is in contrast to previous evidence on testosterone in women. This suggests a sex-specific effect of berberine on sex hormones.
3. Exploring other pathways and sex disparity is worthwhile and has relevance to public health and healthcare.

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## Introduction

In Hong Kong, cardiovascular disease (CVD) is a major disease burden and its rate is higher in men than in women. Berberine is a traditional Chinese medicine; it is an isoquinoline plant alkaloid, belonging to the class of protoberberines. Berberine tablets are extracted from *Coptis chinensis* (Huanglian) and *Phellodendron chinense* (Huangbai) and used in clinical practice for digestive diseases.[1] Berberine has beneficial effects on lowering lipids and fasting glucose in patients with hyperlipidaemia and/or diabetes.[2] Potential benefits of berberine for blood pressure control and adiposity have also been reported in a systematic review,[1] although there is high heterogeneity among studies in terms of study quality and design.[2,3] No serious adverse event has been reported,[1] which suggests good tolerability of berberine supplementation.

Nonetheless, the mechanism by which berberine exerts a protective role in atherosclerosis is unclear. Protoberberines have been identified as a new inhibitor of aldo-keto reductase family 1 member C3 (AKR1C3), an enzyme responsible for regulation of steroid hormone action, such as estrone to 17β-estradiol and androstendione to testosterone, which raises the possibility of action via sex hormones. Accumulating evidence suggests androgens might be a modifiable causal factor underlying men's cardiovascular disadvantage.[4] Berberine also lowers total testosterone in women,[5] although its effect on testosterone in men has not been examined. We hypothesised that berberine might exert its beneficial effects on CVD risk factors by lowering testosterone. We examined the effects of berberine on CVD risk factors, specifically lipids, systolic and diastolic blood pressure, thromboxane A2, and adiposity, as well as the potential mediation via testosterone in Chinese men with hyperlipidaemia.

## Methods

A volunteer sample of 84 Chinese men aged 20 to 65 years with hyperlipidaemia was recruited from staff and/or their families of The University of Hong Kong and from an outpatient clinic in Department of Medicine, Queen Mary Hospital. Hyperlipidaemia was defined as triglycerides >150 mg/dL (1.70 mmol/L), total cholesterol >200 mg/dL (5.16 mmol/L), and/or low-density lipoprotein cholesterol (LDL-c) >100 mg/dL (2.58 mmol/L) according to the National Cholesterol Education Program Adult Treatment Panel II. The volunteers were not receiving hormone replacement therapy such as testosterone replacement therapy in the past 12 months or taking berberine or nutraceuticals that contain berberine. The volunteers were free of any congenital diseases (eg, familial hypercholesterolemia) or any infectious diseases (eg, seasonal influenza) and had no history of any chronic diseases (ischaemic heart disease, myocardial infarction, stroke, diabetes, cancer, and liver/renal dysfunction).

Participants were equally randomised to receive either purified berberine tablets (500 mg) orally twice a day or placebo for 12 weeks. Primary outcomes included lipids (total cholesterol, LDL-c, triglycerides, high-density lipoprotein cholesterol), systolic and diastolic blood pressure, thromboxane A2, and serum testosterone from fasting blood samples. Secondary outcomes included body mass index and waist-hip ratio. Participants were assessed at baseline and at 8 weeks and 12 weeks.

An intention to treat analysis was used. Changes in CVD risk factors were compared between



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TABLE 1. Baseline characteristics of the participants in berberine and placebo groups*

| Characteristic | Berberine group (n=40) | Placebo group (n=40) |
|---|---|---|
| Place of birth | | |
| Hong Kong | 36 (90) | 33 (82.5) |
| Macau | 0 | 2 (5) |
| Mainland China | 4 (10) | 5 (12.5) |
| Education level | | |
| Primary school | 6 (15.0) | 7 (17.5) |
| High school | 25 (62.5) | 20 (50) |
| University and above | 9 (22.5) | 13 (32.5) |
| Smoking status | | |
| Non-smoker | 24 (60) | 30 (75) |
| Ex-smoker | 12 (30) | 5 (12.5) |
| Current smoker | 4 (10) | 5 (12.5) |
| Alcohol drinking | | |
| Never | 6 (15.0) | 8 (20) |
| Ex-drinker | 10 (25.0) | 8 (20) |
| <1 day per week | 15 (37.5) | 15 (37.5) |
| 1-2 days per week | 3 (7.5) | 7 (17.5) |
| 3-7 days per week | 6 (15) | 2 (5) |
| Age, y | 49.5±11.1 | 44.8±13.5 |
| Time of doing physical activity per day, min | | |
| Vigorous | 85.0±43.7 | 71.0±60.9 |
| Moderate | 69.6±51.0 | 76.8±83.9 |
| Light | 67.3±61.2 | 60.0±59.9 |

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

TABLE 2. Effect of berberine on cardiovascular disease risk factors and testosterone

| Cardiovascular disease risk factor | Beta (95% confidence interval) | P value |
|---|---|---|
| Total cholesterol | -0.39 (-0.62 to -0.16) | 0.001 |
| Low-density lipoprotein cholesterol | -0.23 (-0.43 to -0.02) | 0.03 |
| Triglycerides | -0.31 (-0.67 to 0.06) | 0.10 |
| High-density lipoprotein cholesterol | -0.03 (-0.09 to 0.02) | 0.26 |
| Systolic blood pressure | -0.91 (-4.75 to 2.93) | 0.64 |
| Diastolic blood pressure | -0.31 (-3.42 to 2.80) | 0.84 |
| Body mass index | -0.39 (-0.99 to 0.21) | 0.20 |
| Waist-hip ratio | -0.006 (-0.02 to 0.01) | 0.36 |
| Thromboxane A2 | 8.46 (-23.0 to 39.9) | 0.60 |
| Testosterone | 1.31 (0.30 to 2.33) | 0.01 |

the berberine and placebo groups using generalised estimating equation model.

## Results

A total of 84 men were randomly assigned to the berberine group (n=42) and the placebo group (n=42). Two men in each group were lost to follow-up; 40 men in each group were included for analysis (Table 1). After intervention, men taking berberine had a larger reduction in total cholesterol and LDL-c than those taking placebo (Table 2). Changes in other CVD risk factors did not differ between the two groups. Inconsistent with our hypothesis, berberine did not lower testosterone in men but may increase testosterone. Berberine was well-tolerated with no serious adverse event. Headache occurred in one participant in berberine group; diarrhoea occurred in one participant in berberine group; headache, nausea, and vomiting occurred in one participant in placebo group. All adverse events resolved after stopping taking berberine or placebo.

## Discussion

Our findings are consistent with one study that shows a beneficial effect of berberine on total cholesterol and probably LDL-c,[2] but no effect on other CVD risk factors, which is not consistent with other studies,[1,3] although the directions of most effects are beneficial. Moreover, large differences between randomised controlled trials make overall estimates difficult to interpret.[2,3] For example, different trials have varying dosages (from 0.9 g daily to 1.5 g daily), intervention periods (from 1 month to 2 years), and quality.[2] The present study was conducted in men without established CVD or diabetes, in whom berberine may have more effects on CVD risk factors.

In women with polycystic ovary syndrome, supplementation with berberine (1500 mg/d for 3 months) was reported to lower testosterone,[5] although the present study suggests that berberine did not lower testosterone in men. The inconsistency might be due to the differences in dosage or polycystic ovary syndrome. In the present study, berberine tended to increase rather than decrease testosterone in men; berberine appeared to have a differential effect on testosterone by sex. Sex differences in response to drugs is increasingly recognised. Further study in women in the same setting for comparison is warranted to better understand the differential effects of berberine on endocrine factors in men and women.

Our study has several strengths. A pre-specified protocol was followed to avoid selective reporting. Our study for the first time examined the effect of berberine on testosterone and thromboxane

A2 in men. The findings may provide insight into sex-specific effects of berberine. However, there are limitations to the study. The sample size was relatively small, and the findings may not be generalised to other settings. The level of testosterone may vary at different time points of a day, although all samples for assessment were collected in the morning. Thromboxane A2 level in participants varied widely; the null effect may be due to lack of power. Our findings in Chinese men may not apply to other populations with different sex hormone profiles, but the directions of effects are not expected to differ.

## Conclusion

In Chinese men, berberine lowers total cholesterol and probably lowers LDL-c, with good safety and tolerability. Berberine does not lower testosterone in men, which differs from previous evidence on testosterone in women.

## Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#15162621). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

## Disclosure

The results of this research have been previously published in:

1. Zhao JV, Yeung WF, Chan YH, et al. Effect of berberine on cardiovascular disease risk factors: a mechanistic randomized controlled trial. Nutrients 2021;13:2550.

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# Professional-supported, problem-solving, self-learning programme for family carers of people with recent-onset psychosis: abridged secondary publication

**WT Chien *, SY Chan, LK Yip, T Karatzias, D Bressington, ID Lubman**

## KEY MESSAGES

1. The professional-supported, problem-solving, self-learning programme can be an effective intervention for families of people with recent-onset psychosis.
2. The self-learning programme significantly improved family carers' burden, problem-solving ability, and caregiving experiences, as well as patients' psychotic symptoms, recovery, and duration of re-hospitalisation at the 12-month follow-up, compared with family psychoeducation group or usual care.
3. Family caregivers perceived that the intervention could enhance their caregiving skills/abilities of psychosis care, be more positively hopeful for independent family care and patient recovery, and reduce their perceived social stigma.

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## Introduction

Psychosis is a major disabling and disruptive mental illness, affecting over 30% of psychiatric patients worldwide. People with psychosis often have high risks of relapses in the first few years of illness. More than half of them with early-stage psychosis are cared for in the community by their families who often face high levels of physical, psychological, and financial burdens, which can adversely affect their caregiving experiences and general well-being.[1] Although family psychoeducation groups are effective in supporting family caregiving, many families have difficulties in participation owing to time constraints, feelings of stigma to use mental healthcare services, and worrying about other people's negative responses to mental illness.[2,3] We translated (into Chinese) and validated a five-module problem-solving self-learning programme based on an Australian self-help family programme for early psychosis.[2] We aim to evaluate the effects of the self-learning programme for family carers of people with recent-onset psychosis on both carers' and patients' outcomes, compared with the effects of family psychoeducation group or usual psychiatric care.

## Methods

Patients with recent-onset (≤3 years) early-stage psychosis and their family carers aged 18 to 64 years who attended one of the six community centres for mental wellness in Hong Kong were invited to participate. The family carers were living with and caring for the patient for ≥1 year and had a moderate to high caregiving burden (>20 scores of the Family-Burden Interview Schedule).[2] Carers who had recently received family intervention or had a history of a serious mental/medical disease were excluded.

33 families per centre were randomly selected and assigned to the self-learning programme, family psychoeducation group, or usual psychiatric care. To achieve 80% power and 5% significance, 66 patients per group (n=198) were needed to detect a medium effect size on family burden (Cohen's d=0.32), with expected attrition rate of 15%.[2]

Interventions were conducted for family carers over 5 months. The self-learning programme consisted of five modules in Chinese language and four monthly review/sharing group sessions led by a trained nurse facilitator.[2] Family psychoeducation groups were led by one experienced psychiatric nurse based on the validated protocol of psychoeducation group programme.[4] Usual psychiatric care consisted of usual community mental healthcare services provided by psychiatric outpatient clinics and the community centres under study.

Primary outcomes were carers' problem-solving skills (measured by the 25-item Revised Social-Problem-Solving Inventory) and caregiving burden (measured by the 25-item Family Burden



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Interview Schedule), whereas secondary outcomes were caregiving experiences (measured by the 66-item Experience of Caregiving Inventory), psychotic symptoms (measured by the Positive and Negative Syndrome Scale), re-hospitalisation rates, family functioning, and recovery (measured by the Questionnaire about the Process of Recovery). Participants were assessed at baseline (T0) and 1 week (T1), 6 months (T2), and 12 months (T3) after intervention. All tools had satisfactory reliability and validity.[2,4] Four focus-group interviews (3-5 members per group, 15 participants per intervention) were conducted after the 1-week follow-up.

Homogeneity of study groups was examined. Outcomes were analysed based on the intention-to-treat principle. Generalised estimating equations were used to assess the interaction (group × time) effects within and between groups across four time-points (T0-T3), followed by pairwise contrast tests. Missing data were estimated with the maximum likelihood estimation, not having other replacement methods. No co-variance analysis was performed, as there was no significant difference between groups at baseline. Level of statistical significance was set at $P<0.05$. Content analysis was conducted based on group interview data.

## Results

A total of 191 pairs of family carers and patients were included for analysis. The self-learning programme group (n=66), family psychoeducation group (n=66), and usual psychiatric care group (n=66) were comparable in terms of characteristics at baseline (Table 1).

The group × time effect was significant in five outcomes at 12 months after intervention (Wald $\chi^2$=9.68-20.61, P=0.02-0.001, effect size=0.10-0.35, Table 2). Improvement was significantly greater after the self-learning programme than family psychoeducation group or usual psychiatric care. At T1 to T3, compared with usual psychiatric care, self-learning programme achieved greater improvement in caregiving burden (P=0.03-0.002), problem-solving (P=0.04-0.005), psychotic symptoms (P=0.05-0.001), and subjective recovery (P=0.04-0.008). At T2 and T3, compared with usual psychiatric care and family psychoeducation group, self-learning programme achieved greater improvement in mean duration of re-hospitalisations (all P=0.01-0.03). At T3, compared with family psychoeducation group, self-learning programme achieved greater improvement in caregiving burden, problem-solving, psychotic symptoms, and subjective recovery (all P=0.02-0.04).

Compared with family psychoeducation group, self-learning programme achieved greater improvements mainly at T3 in psychotic symptoms (P=0.008), insight (P=0.03), functioning (P=0.01), and recovery level (P=0.005).

Over the three follow-up periods, the percentage of patients being hospitalised reduced from 26.6% (n=17) to 12.5% (n=8) after self-learning programme, from 28.6% (n=18) to 23.8% (n=15) after family psychoeducation group, and slightly increased from 25.0% (n=16) to 29.7% (n=19) after usual psychiatric care. Reduction in the percentage of patients being re-hospitalised from T0 to T3 was greater after self-learning programme than after family psychoeducation group or usual psychiatric care (P=0.005). Types/doses of psychotropic medications and participation in other psychosocial interventions did not differ significantly between the three groups (P>0.20). Mean scores of all outcomes did not differ between community centres (P=0.12-0.20) or between non-completers and completers of self-learning programme (P=0.10-0.21).

Based on the focus-group interviews, three categories of perceived benefits of the self-learning programme were identified: increased caregiving skills and abilities, more positively hopeful for independent family care and patient recovery, and less perceived social stigma. Of the three categories of perceived benefits, two were for the difficulties in intervention participation (concerns about fluctuating psychotic symptoms and long-term persistent treatment needed) and one was for the challenges/hindrances in self-learning and/or problem-solving practices. Only parts of the perceived benefits (enhancing caregiving skills and positively hopeful for independent family care) could be found in family psychoeducation group. Most participants expressed that sharing and support in group sessions encouraged them to continue engaging in the intervention and seek help/information from mental health staff and professionals.

## Discussion

The professional-supported, problem-solving, self-learning (manual-reading) programme for families of people with recent-onset psychosis is effective to improve both carers' and patients' psychosocial health and well-being. Family carers achieved greater improvement in caregiving burden and problem-solving ability, with moderate to large effect sizes (Cohen's d=0.10 and 0.24, respectively). Most of these treatment effects of the self-learning programme were significantly greater than those of the family psychoeducation group, especially at the 12-month follow-up.

These findings suggest that self-learning by family caregivers and group-sharing among those with similar caregiving situations, together with resources provided by health professionals, can provide adequate empowerment, skills, and competence to family carers of people with early psychosis in terms of problem-solving and caregiving skills. These

TABLE 1. Characteristics of participants at baseline (n=198)

| Characteristics | Self-learning programme (n=66) | Family psychoeducation group (n=66) | Usual psychiatric care (n=66) | P value |
|---|---|---|---|---|
| **Family carers** | | | | |
| Sex | | | | 0.22 |
| Female | 41 (62.1) | 42 (63.6) | 44 (66.7) | |
| Male | 25 (37.9) | 24 (36.4) | 22 (33.3) | |
| Age, y | 33.22±8.90 | 36.10±9.12 | 37.50±8.13 | 0.14 |
| 20-29 | 16 (24.2) | 14 (21.2) | 12 (18.2) | |
| 30-39 | 25 (37.9) | 27 (40.9) | 30 (45.5) | |
| 40-49 | 16 (24.2) | 17 (25.8) | 18 (27.3) | |
| ≥50 | 9 (13.6) | 8 (12.1) | 6 (10.0) | |
| Education level | | | | 0.16 |
| Primary school or below | 10 (15.2) | 12 (18.2) | 10 (15.2) | |
| Secondary school | 43 (65.2) | 40 (60.6) | 44 (66.7) | |
| University and post-graduate degree | 13 (19.7) | 14 (21.2) | 12 (18.2) | |
| Relationship with patient | | | | 0.24 |
| Child | 12 (18.2) | 10 (15.2) | 10 (15.2) | |
| Parent | 20 (30.3) | 19 (28.8) | 22 (33.3) | |
| Spouse | 22 (33.3) | 26 (39.4) | 24 (36.4) | |
| Others (eg, sibling) | 12 (18.2) | 11 (16.7) | 10 (15.2) | |
| Monthly household income, HK$ | 16 485±3758 | 17 985±4233 | 17 345±3988 | 0.25 |
| 5000-10 000 | 10 (15.2) | 9 (13.6) | 9 (13.6) | |
| 10 001-15 000 | 25 (37.9) | 22 (33.3) | 21 (31.8) | |
| 15 001-25 000 | 22 (33.3) | 26 (39.4) | 26 (39.6) | |
| 25 001-35 000 | 9 (13.6) | 9 (13.6) | 10 (15.2) | |
| **Patients** | | | | |
| Sex | | | | 0.22 |
| Female | 31 (47.0) | 30 (45.5) | 29 (43.9) | |
| Male | 35 (53.0) | 36 (54.5) | 37 (56.1) | |
| Age, y | 24.48±5.89 | 26.43±6.62 | 28.70±6.98 | 0.27 |
| 18-23 | 29 (43.9) | 27 (41.0) | 25 (37.9) | |
| 24-30 | 28 (42.5) | 33 (50.0) | 34 (51.5) | |
| 31-38 | 9 (13.6) | 6 (10.0) | 7 (10.6) | |
| Employment status | | | | 0.17 |
| Employed (full-time) | 31 (47.0) | 30 (45.5) | 26 (39.4) | |
| Employed (part-time) | 22 (33.3) | 25 (37.9) | 30 (45.5) | |
| Unemployed | 13 (19.7) | 11 (16.7) | 10 (15.2) | |
| Education level | | | | 0.12 |
| Primary school | 12 (18.1) | 10 (15.2) | 13 (19.7) | |
| Secondary school | 36 (54.6) | 40 (60.6) | 35 (53.0) | |
| University/College | 18 (27.3) | 16 (24.2) | 18 (27.3) | |
| Duration of illness, m | 10.82±5.72 | 9.72±5.81 | 11.23±5.85 | 0.18 |
| 1-6 | 17 (25.8) | 15 (22.7) | 16 (24.2) | |
| >6-12 | 30 (45.5) | 31 (47.0) | 30 (45.5) | |
| >12-18 | 19 (28.8) | 20 (30.3) | 20 (30.3) | |
| Services receiving | | | | 0.14 |
| Outpatient department | 60 (90.9) | 58 (87.9) | 56 (84.9) | |
| Day hospital/centre | 7 (10.6) | 10 (15.2) | 9 (13.6) | |
| Community psychiatric nursing service/ early assessment services for young people | 50 (75.8) | 45 (68.2) | 48 (72.7) | |
| Counselling and social/recreational service | 10 (15.2) | 12 (18.2) | 15 (22.7) | |
| Dosage of medication | | | | 0.11 |
| High | 14 (21.2) | 13 (19.7) | 15 (22.7) | |
| Medium | 26 (39.4) | 29 (43.9) | 28 (42.4) | |
| Low | 26 (39.4) | 24 (36.4) | 23 (34.9) | |
| Types of psychotropic drugs | | | | 0.14 |
| Atypical antipsychotic | 25 (37.9) | 27 (40.9) | 25 (37.9) | |
| Typical antipsychotic | 25 (37.9) | 22 (33.3) | 26 (39.4) | |
| Blended antipsychotics | 15 (22.7) | 16 (24.3) | 14 (21.2) | |
| Antidepressant/mood stabiliser | 9 (13.6) | 10 (15.2) | 10 (15.2) | |
| Others (eg, anxiolytics) | 12 (18.2) | 10 (15.2) | 7 (10.6) | |

TABLE 2. Outcome measure scores of the three groups at baseline (T0) and 1 week (T1), 6 months (T2), and 12 months (T3) after intervention (n=191)

| Outcome measure | Self-learning programme (n=64) | Family psychoeducation group (n=63) | Usual psychiatric care (n=64) | Group effect β (95% CI) | Time effect β (95% CI) | Group × time effect β (95% CI) |
|---|---|---|---|---|---|---|
| | Mean±standard deviation (95% confidence interval [CI]) | | | | | |
| Family Burden Interview Schedule | | | | 0.55 (0.30-0.80), P=0.01 | -0.66 (-0.96 to -0.36), P=0.001 | -2.01 (-3.50 to -0.39), P=0.005, Wald $\chi^2$=17.61, effect size=0.24 |
| T0 | 29.13±5.01 (23.89-34.43) | 29.98±6.18 (23.51-36.60) | 29.90±5.76 (22.10-36.74) | | | |
| T1 | 27.03±4.98 (22.11-32.08) | 27.40±6.01 (21.40-33.45) | 30.01±6.03 (23.98-36.08) | | | |
| T2 | 25.41±5.81 (19.52-31.14) | 27.04±5.95 (21.12-32.52) | 29.63±7.12 (22.01-38.05) | | | |
| T3 | 21.82±5.02 (16.02-28.12) | 25.13±7.02 (18.21-32.50) | 31.94±8.01 (23.63-40.05) | | | |
| Experience of Caregiving Inventory | | | | 0.40 (0.20-0.60), P=0.04 | -0.44 (-0.80 to -0.08), P=0.05 | -0.68 (-1.43 to 0.07), P=0.05, Wald $\chi^2$=8.12, effect size=0.05 |
| T0 | 131.22±17.11 (114.11-148.32) | 127.98±18.91 (109.05-148.85) | 123.71±16.81 (106.90-140.65) | | | |
| T1 | 127.21±16.43 (110.80-143.92) | 123.22±16.52 (107.52-140.83) | 130.02±18.42 (111.60-148.52) | | | |
| T2 | 119.23±18.04 (101.20-137.32) | 125.83±20.04 (105.82-145.42) | 129.52±22.02 (107.40-153.54) | | | |
| T3 | 118.84±16.41 (102.52-135.33) | 120.53±18.81 (101.72-139.05) | 130.81±19.21 (111.60-150.42) | | | |
| Social Problem Solving Inventory-Revised: short version | | | | 0.40 (0.12-0.68), P=0.03 | 0.45 (0.20-0.65), P=0.01 | 0.80 (0.30-1.30), P=0.01, Wald $\chi^2$=9.68, effect size=0.10 |
| T0 | 48.33±8.56 (39.80-56.90) | 50.11±7.93 (42.31-58.05) | 50.08±6.80 (43.30-56.95) | | | |
| T1 | 52.22±8.46 (43.82-60.83) | 52.23±7.03 (45.11-59.28) | 49.02±8.04 (41.08-57.26) | | | |
| T2 | 55.23±9.02 (46.24-63.35) | 53.02±9.16 (43.89-62.36) | 50.01±9.51 (40.50-59.62) | | | |
| T3 | 58.85±8.43 (50.43-65.39) | 54.82±9.05 (44.80-63.89) | 49.83±10.23 (39.70-60.16) | | | |
| No. of re-hospitalisations | | | | 0.21 (0.10-0.32), P=0.09 | 0.23 (0.15-0.29), P=0.08 | 0.46 (0.10-0.72), P=0.10, Wald $\chi^2$=2.07, effect size=0.02 |
| T0 | 1.72±1.10 (0.60-2.84) | 1.70±1.01 (0.70-2.73) | 1.57±0.92 (0.63-2.54) | | | |
| T1 | 1.58±0.98 (0.60-2.58) | 1.52±1.01 (0.50-2.54) | 1.79±0.90 (0.89-2.70) | | | |
| T2 | 1.63±0.81 (0.81-2.34) | 1.65±1.00 (0.65-2.65) | 1.60±1.14 (0.48-2.75) | | | |
| T3 | 1.34±0.86 (0.50-2.21) | 1.70±1.22 (0.49-2.93) | 1.50±1.31 (0.18-2.82) | | | |
| Duration of re-hospitalisation, d | | | | -0.38 (-0.60 to -0.26), P=0.04 | -0.50 (-0.84 to -0.16), P=0.01 | -0.87 (-1.30 to -0.30), P=0.02, Wald $\chi^2$=9.71, effect size=0.10 |
| T0 | 16.98±6.01 (10.82-23.11) | 19.78±7.52 (12.12-27.44) | 17.85±7.90 (9.87-25.55) | | | |
| T1 | 14.02±5.85 (8.20-19.91) | 16.33±6.44 (10.00-22.74) | 15.91±7.12 (8.79-23.03) | | | |
| T2 | 12.08±6.21 (5.90-18.32) | 17.21±9.02 (8.21-26.25) | 17.83±9.51 (8.32-27.14) | | | |
| T3 | 14.15±8.53 (5.62-22.65) | 18.02±9.04 (9.00-27.10) | 18.55±10.11 (8.45-28.66) | | | |

TABLE 2. (cont'd)

| Outcome measure | Self-learning programme (n=64) | Family psychoeducation group (n=63) | Usual psychiatric care (n=64) | Group effect β (95% CI) | Time effect β (95% CI) | Group × time effect β (95% CI) |
|---|---|---|---|---|---|---|
| | Mean±standard deviation (95% confidence interval [CI]) | | | | | |
| No. of patients being hospitalised | | | | | | Kruskal-Wallis test=7.81, P=0.005 |
| T0 | 17 | 18 | 17 | | | |
| T1 | 14 | 14 | 16 | | | |
| T2 | 12 | 15 | 19 | | | |
| T3 | 8 | 15 | 17 | | | |
| Positive and Negative Syndrome Scale | | | | -0.68 (-0.98 to -0.38), P=0.005 | -0.72 (-1.13 to -0.29), P=0.002 | -1.35 (-1.96 to -0.74), P=0.001, Wald $\chi^2$=20.61, effect size=0.35 |
| T0 | 130.56±17.01 (112.40-147.68) | 133.85±20.29 (113.51-123.63) | 132.78±22.30 (110.51-155.13) | | | |
| T1 | 116.53±17.82 (98.52-135.53) | 117.22±14.71 (102.51-131.83) | 128.12±9.81 (119.01-137.93) | | | |
| T2 | 99.64±19.24 (80.03-119.02) | 108.81±12.21 (96.60-121.02) | 129.21±17.10 (112.10-146.32) | | | |
| T3 | 88.22±17.05 (71.03-106.25) | 100.11±19.51 (80.10-119.73) | 130.82±19.81 (111.01-150.65) | | | |
| Questionnaire about the Process of Recovery | | | | 0.62 (0.23-1.01), P=0.008 | 0.58 (0.25-0.91), P=0.01 | 1.20 (0.89-1.51), P=0.003, Wald $\chi^2$=17.10, effect size=0.28 |
| T0 | 38.89±9.04 (29.83-37.95) | 39.12±9.03 (30.08-48.26) | 37.89±9.12 (28.77-37.22) | | | |
| T1 | 41.92±9.01 (32.91-40.94) | 39.21±9.10 (30.11-48.22) | 38.12±8.50 (29.88-36.62) | | | |
| T2 | 43.57±9.82 (33.75-43.34) | 40.81±8.21 (32.60-49.02) | 37.08±9.81 (22.27-46.89) | | | |
| T3 | 46.24±11.05 (35.19-57.39) | 42.50±9.22 (33.28-51.73) | 39.02±8.31 (30.21-47.33) | | | |

self-learning and guided practices can be more helpful than the didactic education or information giving in psychoeducation programmes.[1,5] These findings are echoed by the perceived benefits of the self-learning programme identified by focus-group interviews. Furthermore, self-learning and mutual sharing of illness management, together with effective problem-solving, are increasingly important in family intervention for severe mental illness, particularly for first-time carers.[1-5]

The self-learning programme (and family psychoeducation group) had a very high completion rate and a low attrition rate over the 12-month follow-up. The self-learning programme is more structured than other self-help or mutual support groups that combines social support and family psychoeducation principles and materials with problem-solving and stress management approaches.[2,5] The self-learning programme has favourable effects on various psychosocial health outcomes over a long term; it is user-friendly and less costly in terms of manpower and resources. Our self-learning programme is more successful than other family interventions that have 40% to 90% of completion rate and 12% to 50% of attrition rate.[1,5]

There are limitations to the present study. Participants were volunteers and thus were likely to be more motivated for intervention engagement; they were not blinded to the intervention allocation and there may be expectation or response bias. The carers and patients recruited had relatively high education level, above average household income, and short duration of illness, and were from only six of 25 community centres in Hong Kong. Thus, generalisability of the findings may be reduced. The self-learning programme only involved one primary carer and minimal participation by patients. Thus, the family-dyad effect was limited. The extent of

engagement and consistency of module learning and/or problem-solving practices were not known and thus further study of these co-variant effects is warranted.

## Conclusion

The professional-supported self-learning programme for family carers of people with recent-onset psychosis is effective to improve both carers' and patients' psychosocial health and mental well-being and hence to reduce patient relapse from psychosis. Future longitudinal study is warranted to investigate associations between perceived benefits, skills performance (mediator), and therapeutic mechanisms of the self-learning programme, using structural modelling and qualitative interviews/observations.

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## Disclosure

The results of this research have been previously published in:

1. Chien WT, Bressington D, Lubman DI, Karatzias T. A randomised controlled trial of a caregiver-facilitated problem-solving based self-learning program for family carers of people with early psychosis. Int J Environ Res Public Health 2020;17:9343.
2. Chien WT, Yip LK, Lubman DI. A randomized controlled trial of a nurse-assisted problem-solving-based self-learning program for family caregivers in recent-onset psychosis. Int J Adv Sci Eng Technol 2019;7(S2):23-7.

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