SUPPLEMENT 7

HONG KONG MEDICAL JOURNAL 香港醫學雜誌 Volume 30 Number 6 December 2024 30(S7)

HONG KONG Volume 30 Number 6 December 2024

MEDICAL JOURNAL
香港醫學雜誌

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

Health and Medical Research Fund
Research Dissemination Reports
醫療衞生研究基金
研究成果報告

Infectious diseases
傳染病

Preventive medicine
預防醫學

Mental health
精神健康

Cancer
癌症

Liver diseases
肝臟疾病

Advanced technology
先進科技

Supplement 7

ISSN 1024-2708

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

HONG KONG MEDICAL JOURNAL 香港醫學雜誌
Volume 30 Number 6 **December 2024**
SUPPLEMENT 7

Health and Medical Research Fund

Research Dissemination Reports

LIVER DISEASES

ADVANCED TECHNOLOGY

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 10 dissemination reports of projects related to infectious diseases, preventive medicine, mental health, cancer, liver diseases, and advanced technology. In particular, research findings of three projects may provide insights to enhance clinical practices and help inform health policy formulation in Hong Kong.

Seasonal influenza epidemics are a major cause of severe illness and death around the world with older adults being mainly affected. Seasonal influenza vaccination is safe and effective, but uptake is low among older adults in Hong Kong. Wang et al[1] developed a seasonal influenza vaccination promotion programme based on a chatbot that delivers customised intervention pathways according to the participants' stage-of-change regarding vaccine uptake and their responses to various questions and prompts. They conducted a randomised controlled trial comparing the efficacy between the online stage-customised intervention and a standard non-stage-customised online intervention among nearly 400 Chinese-speaking community-dwelling elders aged >65 years who had not received the upcoming seasonal influenza vaccine. Six months after the intervention, the seasonal influenza vaccine uptake rate was higher in the intervention group than in the control group (50.5% vs 35.4%, P=0.002). The chatbot-based intervention was a highly feasible and acceptable tool for promoting health among older adults.

Metabolic syndrome is associated with elevated risks of diabetes, prediabetes, and cardiovascular disease. E-health technology via mobile phones is an effective way of delivering educational interventions to support patients with diabetes or metabolic syndrome. Leung et al[2] incorporated a custom-designed mobile application (app) into an existing lifestyle intervention programme for patients with metabolic syndrome. They conducted a randomised controlled trial comparing health-related outcomes over 24 weeks among 264 Chinese patients with metabolic syndrome who received the health-education programme via mobile app, booklet, or usual care. Compared to usual care, both the app- and booklet-based interventions led to significantly greater reductions in body weight, waist circumference, body mass index, and systolic blood pressure, as well as increased total exercise time and amount, within 24 weeks.

Psychosis is a serious mental health condition and is associated with a high risk of relapse in the early stages of illness. Psychosocial interventions can help improve symptoms and reduce relapses. Chien et al[3] evaluated the effectiveness of a peer-support, worker-led, self-management programme compared with psychoeducation and treatment-as-usual in a multicentre, three-arm, randomised controlled trial among 480 Chinese adults with recent-onset psychotic disorder. The peer-led programme, in addition to usual care, was an effective intervention for people with recent-onset psychosis and significantly improved patients' recovery during long-term follow-up. The peer-led programme significantly improved patients' functioning, symptoms, illness insight, and service satisfaction, as well as reduced re-hospitalisation rates over an 18-month follow-up period compared with psychoeducation or usual care alone.

Supplement editors

Dr Anne Fung
Head
Research and Data Analytics Office
Health Bureau

Dr Richard A Collins
Senior Scientific Reviewer
Research and Data Analytics Office
Health Bureau

References

1. Wang Z, Lau JTF, Mo PKH, Zhang Q, Wong MCS. Online intervention to increase seasonal influenza vaccination among community-dwelling older people: a randomised controlled trial (abridged secondary publication). Hong Kong Med J 2024;30(Suppl 7):S4-8.
2. Leung DYP, Wong EML, Leung AMY, Cheung ASP, Cheung KC. Lifestyle intervention using a mobile application versus booklet for adults with metabolic syndrome: a multicentre randomised controlled trial (abridged secondary publication). Hong Kong Med J 2024;30(Suppl 7):S12-6.
3. Chien WT, Bressington D, Gray R, Chan SY, Lubman DI. Peer-led self-management programme for people with recent-onset onset psychosis: a randomised controlled trial (abridged secondary publication). Hong Kong Med J 2024;30(Suppl 7):S22-7.

Online intervention to increase seasonal influenza vaccination among community-dwelling older people: a randomised controlled trial (abridged secondary publication)

Z Wang *, JTF Lau, PKH Mo, Q Zhang, MCS Wong

KEY MESSAGES

1. A stage-customised online intervention based on the trans-theoretical model was more effective than a standard, non-stage-customised online intervention in increasing seasonal influenza vaccination uptake among community-dwelling individuals aged ≥65 years.
2. Compliance with the intervention and changes in constructs of the trans-theoretical model fully or partially mediated the effects of the intervention.
3. A WhatsApp-based chatbot was a highly feasible and acceptable tool for promoting health among older adults.

Hong Kong Med J 2024;30(Suppl 7):S4-8
HMRF project number: 19181152

[1] Z Wang, [1] JTF Lau, [1] PKH Mo, [2] Q Zhang, [1] MCS Wong

[1] *Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, China*
[2] *School of Data Science, City University of Hong Kong, Hong Kong SAR, China*

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

Introduction

Seasonal influenza epidemics cause 3 to 5 million cases of severe illness and 290 000 to 650 000 deaths annually worldwide.[1] In Hong Kong, the flu season usually lasts from January to March and from July to August[2]; severe illness and death mainly affect individuals aged ≥65 years.[3] Seasonal influenza was a serious health threat during the COVID-19 pandemic.[4] Seasonal influenza vaccination (SIV) is effective and safe for older adults. However, SIV coverage remains low among older adults in Hong Kong.

The trans-theoretical model (TTM) was used to guide the development of our SIV uptake promotion.[5] A chatbot is a programme that can automatically select and deliver customised intervention pathways according to participants' responses, enabling the provision of personalised, engaging, and on-demand health promotion. A chatbot can be designed to deliver a customised online intervention for promoting SIV among older adults. It can assess a user's stage of change (SOC) regarding SIV uptake and disseminate customised interventions through instant messaging platforms (eg, WhatsApp). This fully automated approach is cost-effective and can deliver multiple sessions of stage-customised intervention.

This randomised controlled trial was conducted to compare the efficacy between a stage-customised online intervention and a standard, non-stage-customised online intervention in promoting SIV uptake among community-dwelling individuals aged ≥65 years. Additionally, we evaluated the efficacy of the intervention in increasing behavioural intention to receive SIV and in modifying constructs related to the TTM during follow-up.

Methods

A non-blinded, two-arm parallel randomised controlled trail was conducted in Hong Kong between November 2021 and July 2022. Community-dwelling, Chinese-speaking older adults aged ≥65 years who owned a smartphone and had not received SIV for the upcoming flu season were invited to participate through random telephone sampling. Individuals who had cognitive impairment, blindness or deafness, inability to communicate with others effectively, or known contraindications for SIV were excluded.

Household numbers were randomly selected from the most recent telephone directories. In households with more than one person aged ≥65 years, the individual whose last birthday was closest to the interview date was invited to participate. Participants were randomly assigned to either the intervention group or the control group via the chatbot algorithm. Participants were interviewed by telephone at baseline and at 3 and 6 months after completion of the intervention.

In the control group, the chatbot provided a link to access a standard online video (approximately 2 minutes) covering basic information about SIV (who, when, and where to receive SIV) at weeks 0, 2, 4, and 6. In the intervention group, the chatbot delivered one of several SOC-customised online health promotion videos regarding SIV uptake, once every 2 weeks for four sessions, through WhatsApp at weeks 0, 2, 4, and 6. At the start of each session, the chatbot assessed the participant's

SOC. Beginning with the second session, the chatbot also asked whether the participant had received SIV for the upcoming flu season. If the participant clicked 'yes', the chatbot recorded this response and automatically ended the programme. Otherwise, the chatbot provided a link to an SOC-customised health promotion video through WhatsApp.

The primary outcome measure was the prevalence of self-reported seasonal influenza vaccine uptake at month 6. This outcome was validated by requesting participants to upload an image of their SIV receipt. Secondary outcome measures included behavioural intention to receive SIV in the next year, perceived pros and cons and self-efficacy of SIV, SOC related to SIV, and compliance with the intervention.

An intention-to-treat analysis was performed. Missing data regarding SIV uptake were treated as non-uptake. The Markov Chain Monte Carlo method was used to impute missing data regarding secondary outcomes. Chi-square tests or independent-samples *t* tests were used to compare the groups. Relative and absolute risk reductions and the number needed to treat were calculated. Logistic regression (for binary variables) and linear regression models (for continuous variables) were used to explore between-group difference in outcomes after adjustment for any confounders. We evaluated whether changes in SOC, perceived pros and cons, and self-efficacy mediated between-group differences in the prevalence of SIV uptake at month 6. Hypotheses were tested using the Baron and Kenny's approach.

Results

Of 3963 households contacted, 698 included an eligible older adult. Of these, 396 (56.7%) completed the baseline telephone survey and were randomly assigned to either the intervention group (n=198) or the control group (n=198). At month 6, 339 participants completed the telephone follow-up survey; the dropout rates were 14.4% overall, 16.7% in the control group, and 12.1% in the intervention group. Participants with no history of SIV or pneumococcal vaccination or with fewer doses of SIV in the past 3 years were more likely to drop out.

The control and intervention groups were comparable in terms of all baseline characteristics, except for the Perceived Self-efficacy Scale score (P=0.03, Table 1). At month 6, the SIV uptake rate was higher in the intervention group than in the control group (50.5% vs 35.4%, relative risk reduction=1.43, absolute risk reduction=0.15, number needed to treat=6.6, P=0.002, Table 2).

At month 6, the intervention group had larger proportions of participants who completed at least one episode of intervention (77.3% vs 62.6%, P<0.001), were at a higher SOC (P=0.001), and reported higher perceived pros (P=0.001) and self-efficacy (P=0.01) but lower perceived cons (P=0.002). Regarding changes in perception based on the TTM, the intervention group displayed a smaller increase in Perceived Cons Scale score (P=0.02), smaller decreases in Perceived Pros Scale score (P=0.007) and Perceived Self-Efficacy Scale score (P=0.01), and a larger increase in SOC (P=0.01) [Table 3]. However, the two groups were comparable in terms of behavioural intention to receive SIV in the next 6 months among participants who had not received SIV (39.8% vs 35.9%, P=0.56).

After adjusting for changes in self-efficacy and SOC, the association between intervention status and SIV uptake was no longer significant. This suggests that changes in self-efficacy and SOC mediated the effect of intervention. The association between intervention status and SIV uptake also weakened after adjusting for changes in perceived pros (from P=0.001 to P=0.01), perceived cons (from P=0.001 to P=0.02), and completion of at least one episode of intervention (from P=0.001 to P=0.01). Perceived pros, perceived cons, and completion of at least one episode of intervention remained significant (P<0.001), which indicated partial mediation.

Discussion

Our study evaluated the efficacy of a chatbot-delivered, theory-based intervention to increase SIV uptake among community-dwelling older adults in Hong Kong. Compared with the control group, the intervention group showed a significant increase in SIV uptake. Our intervention was fully automated and required minimal resources to implement or maintain. The chatbot can be easily integrated with governmental webpages that provide SIV-related information, as well as WhatsApp groups.

A WhatsApp-based chatbot was acceptable for delivering health promotion to older adults. The chatbot-delivered intervention was well-received, and most participants did not encounter any difficulties in using the chatbot. The level of compliance with the intervention, changes in SOC, and changes in perceived pros and cons and self-efficacy mediated the effect of intervention. These results also extended the applicability of the TTM.

This study had several limitations. First, the COVID-19 pandemic and COVID-19 vaccine rollout might have influenced the study outcome. Nonetheless, these effects were expected to be similar across the two groups. Second, participation was limited to older adults with smartphone access. Third, people aged ≥75 years were under-sampled. Fourth, selection bias may have resulted from non-responses. Fifth, attrition bias might be present because those who dropped out of the intervention group were less likely to report a history of SIV at baseline, compared with those who did not drop out. However, our study's strengths included a population-based representative

TABLE 1. Baseline characteristics of participants and seasonal influenza vaccination (SIV) uptake

Characteristic	All (n=396)*	Intervention group (n=198)*	Control group (n=198)*	P value
Age, y				0.78
65-69	201 (50.8)	104 (52.5)	97 (49.0)	
70-74	134 (33.8)	65 (32.8)	69 (34.8)	
≥75	61 (15.4)	29 (14.6)	32 (16.2)	
Sex				0.12
Male	147 (37.1)	81 (40.9)	66 (33.3)	
Female	249 (62.9)	117 (59.1)	132 (66.7)	
Relationship status				0.17
Currently single	106 (26.8)	47 (23.7)	59 (29.8)	
Married or cohabiting with a partner	290 (73.2)	151 (76.3)	139 (70.2)	
Education level				0.54
Primary or below	164 (41.4)	86 (43.4)	78 (39.4)	
Secondary	189 (47.7)	89 (44.9)	100 (50.5)	
Tertiary or above	43 (10.9)	23 (11.6)	20 (10.1)	
Monthly household income, HK$				0.70
<20 000	294 (74.2)	144 (72.7)	150 (76.1)	
≥20 000	52 (13.1)	27 (13.6)	25 (12.7)	
Undisclosed	50 (12.6)	27 (13.6)	23 (11.6)	
Receiving Comprehensive Social Security Assistance				0.45
No	366 (92.4)	185 (93.4)	181 (91.4)	
Yes	30 (7.6)	13 (6.6)	17 (8.6)	
Living alone				0.52
No	321 (81.1)	158 (79.8)	163 (82.3)	
Yes	75 (18.9)	40 (20.2)	35 (17.7)	
Smoking in the past year				0.84
No	369 (93.2)	185 (93.4)	184 (92.9)	
Yes	27 (6.8)	13 (6.6)	14 (7.1)	
Binge drinking in the past year				0.74
No	387 (97.7)	194 (98.0)	193 (97.5)	
Yes	9 (2.3)	4 (2.0)	5 (2.5)	
Comorbidity				
Hypertension	189 (47.7)	100 (50.5)	89 (44.9)	0.27
Chronic cardiovascular diseases	42 (10.6)	19 (9.6)	23 (11.6)	0.51
Chronic lung diseases	8 (2.0)	6 (3.0)	2 (1.0)	0.15
Chronic liver diseases	8 (2.0)	5 (2.5)	3 (1.5)	0.48
Chronic kidney diseases	3 (0.8)	2 (1.0)	1 (0.5)	0.56
Diabetes mellitus	75 (18.9)	39 (19.7)	36 (18.2)	0.70
Any of above	239 (60.4)	127 (64.1)	112 (56.6)	0.12
History of COVID-19				0.41
No	390 (98.5)	196 (99.0)	194 (98.0)	
Yes	6 (1.5)	2 (1.0)	4 (2.0)	
History of SIV				0.18
No	159 (40.2)	73 (36.9)	86 (43.4)	
Yes	237 (59.8)	125 (63.1)	112 (56.6)	

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

TABLE 1. (cont'd)

Characteristic	All (n=396)*	Intervention group (n=198)*	Control group (n=198)*	P value
No. of doses of SIV received in the past 3 years				0.21
0	180 (45.5)	86 (43.4)	94 (47.5)	
1	33 (8.3)	14 (7.1)	19 (9.6)	
2	48 (12.1)	21 (10.6)	27 (13.6)	
3	135 (34.1)	77 (38.9)	58 (29.3)	
History of pneumococcal vaccination				0.73
No	293 (74.0)	145 (73.2)	148 (74.7)	
Yes	103 (26.0)	53 (26.8)	50 (25.3)	
No. of doses of COVID-19 vaccine received				0.76
0	153 (38.6)	76 (38.4)	77 (38.9)	
1	8 (2.0)	3 (1.5)	5 (2.5)	
2	235 (59.3)	119 (60.1)	116 (58.6)	
Perceived pros of SIV				
SIV is highly effective in protecting me from seasonal influenza	253 (63.9)	130 (65.7)	123 (62.1)	0.46
SIV is highly effective in preventing severe consequences of seasonal influenza	272 (68.7)	141 (71.2)	131 (66.2)	0.28
SIV is highly effective in protecting my family members from seasonal influenza	194 (49.0)	97 (49.0)	97 (49.0)	1.00
Perceived Pros Scale score	7.4±1.8	7.5±1.7	7.4±1.8	0.78
Perceived cons of SIV				
SIV has severe side effects	28 (7.1)	11 (5.6)	17 (8.6)	0.24
SIV is too expensive for me	8 (2.0)	3 (1.5)	5 (2.5)	0.48
It is inconvenient for me to receive SIV	13 (3.3)	7 (3.5)	6 (3.0)	0.78
My health conditions are not suitable for receiving SIV	65 (16.4)	34 (17.2)	31 (15.7)	0.68
SIV would negatively impact the effectiveness of COVID-19 vaccination	24 (6.1)	11 (5.6)	13 (6.6)	0.67
COVID-19 vaccination would negatively impact the effectiveness of SIV	21 (5.3)	10 (5.1)	11 (5.6)	0.82
Perceived Cons Scale score	8.5±1.8	8.5±1.7	8.6±1.9	0.33
Perceived self-efficacy related to SIV				
I am confident in receiving SIV (if I want to receive it)	378 (95.5)	185 (93.4)	193 (97.5)	0.054
Receiving SIV is easy for me	372 (93.9)	181 (92.4)	191 (96.5)	0.08
Perceived Self-efficacy Scale score	5.9±0.6	5.8±0.8	5.9±0.4	0.03
Stage of change related to SIV				0.12
Pre-contemplation stage	148 (37.4)	64 (32.3)	84 (42.4)	
Contemplation stage	87 (22.0)	48 (24.2)	39 (19.7)	
Preparation stage	161 (40.7)	86 (43.4)	75 (37.9)	

sample, a well-validated primary outcome, and a relatively low dropout rate.

Conclusion

A chatbot-delivered, stage-customised online intervention was more effective than a chatbot-delivered, non-stage-customised intervention in increasing SIV uptake among community-dwelling individuals aged ≥65 years.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#19181152). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

TABLE 2. Seasonal influenza vaccination (SIV) uptake within 6 months and behavioural intention to receive SIV in the next 6 months

Variable	Inter-vention	Control	Relative risk reduction (95% confidence interval)	P value	Absolute risk reduction (95% confidence interval)	Number needed to treat (95% confidence interval)	Adjusted odds ratios (95% confidence interval	P value
SIV uptake, %								
All participants	50.5	35.4	1.43 (1.13-1.80)	0.002	0.15 (0.06-0.25)	6.6 (4.0-18.1)	1.96 (1.30-2.94)	0.001
Those with no history of SIV at baseline	9.6	10.5	0.92 (0.36-2.34)	0.86	-0.01 (-0.10-0.08)	-114.1 (-9.8-11.8)	0.83 (0.28-2.40)	0.73
Those with a history of SIV at baseline	74.4	54.5	1.37 (1.12-1.67)	0.001	0.19 (0.08-0.32)	5.1 (3.1-12.6)	2.66 (1.52-4.67)	0.001
Behavioural intention to receive SIV in the next 6 months among those who had not received SIV, %	39.8	35.9	1.11 (0.79-1.55)	0.55	0.04 (-0.08-0.17)	25.9 (-11.2-6.0)	1.18 (0.68-2.04)	0.56

TABLE 3. Between-group differences in perceived pros and cons and self-efficacy, as well as stage of change, related to seasonal influenza vaccination uptake

Variable	Intervention group (n=198)	Control group (n=198)	Adjusted β	P value
Perceived Pros Scale score				
Baseline	7.5±1.7	7.4±1.8	0.02	0.76
Month 6	6.9±2.3	6.1±2.6	0.17	0.001
Month 6 - baseline	-0.6±2.4	-1.3±3.1	0.14	0.007
Perceived Cons Scale score				
Baseline	8.5±1.7	8.6±1.9	-0.07	0.14
Month 6	10.2±3.5	11.1±3.4	-0.15	0.002
Month 6 – baseline	1.7±3.3	2.5±3.3	-0.12	0.02
Perceived Self-efficacy Scale score				
Baseline	5.8±0.8	5.9±0.4	-0.11	0.03
Month 6	4.4±1.8	3.9±1.7	0.14	0.01
Month 6 – baseline	-1.4±1.8	-2.0±1.7	0.14	0.01
Stage of change				
Baseline	2.1±0.9	2.0±0.9	0.09	0.08
Month 6	2.8±1.3	2.3±1.3	0.17	0.001
Month 6 - baseline	0.7±1.0	0.3±1.0	0.13	0.01

Disclosure

The results of this research have been previously published in:

1. Wang Z, Chan PS, Fang Y, et al. Chatbot-delivered online intervention to promote seasonal influenza vaccination during the COVID-19 pandemic: a randomized clinical trial. JAMA Netw Open 2023;6:e2332568.

References

1. World Health Organization. Fact Sheets: Influenza (seasonal). Accessed 30 November 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).
2. Centre for Health Protection. Recommendation on Seasonal Influenza Vaccination for the 2018/19 season in Hong Kong. Accessed 30 November 2022. Available from: https://www.chp.gov.hk/files/pdf/scvpd_recommendations_on_siv_for_2018_19_season.pdf.
3. Centre for Health Protection. Seasonal influenza vaccination & pneumococcal vaccination. Accessed 30 November 2022. Available from: https://www.chp.gov.hk/files/pdf/1sivandpv.pdf.
4. The Government of the Hong Kong SAR. End of winter influenza season 2020. Accessed 30 November 2022. Available from: https://www.info.gov.hk/gia/general/202002/13/P2020021300600.htm.
5. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot 1997;12:38-48.

Increasing rotavirus vaccine uptake in children: a randomised controlled trial (abridged secondary publication)

KHT Yeung, WH Tam, GPG Fung, EAS Nelson *

KEY MESSAGES

1. An intervention package containing a voucher for free rotavirus vaccine, key information about rotavirus, and vaccination reminders increased rotavirus vaccine uptake among Hong Kong children by 1.7-fold or 33 percentage points (from 48% to 81%), regardless of mothers' initial plans concerning rotavirus vaccination during the immediate postpartum period.
2. The effect of the intervention package was greatest in low-income families. This indicates that removal of financial barriers to vaccination may promote vaccine uptake equity.
3. The provision of key information about rotavirus and vaccination reminders substantially increased vaccine uptake in lower-income families potentially by enhancing mothers' perceptions of rotavirus vaccine benefits and their self-efficacy.
4. The intervention package strengthened mothers' confidence in decision to vaccinate their children.
5. In the absence of the voucher for rotavirus vaccination, the main reason mothers cited for not vaccinating their children was that the vaccine is excluded from Hong Kong's routine Childhood Immunisation Programme.

Hong Kong Med J 2024;30(Suppl 7):S9-11
HMRF project number: 19180202

[1] KHT Yeung, [2] WH Tam, [1] GPG Fung, [1,3] EAS Nelson

[1] *Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong SAR, China*
[2] *Department of Obstetrics and Gynaecology, The Chinese University of Hong Kong, Hong Kong SAR, China*
[3] *School of Medicine, The Chinese University of Hong Kong, Shenzhen, Guangdong, China*

* Principal applicant and corresponding author: tony-nelson@cuhk.edu.hk

Introduction

The rotavirus vaccine is safe and effective against hospitalisation and is cost-saving.[1,2] However, it has not been included in Hong Kong's Childhood Immunisation Programme. This randomised controlled trial examined whether an intervention package involving (1) removal of financial barriers and/or (2) provision of key information about rotavirus, along with vaccination reminders, could increase rotavirus vaccine uptake among Hong Kong children.

Methods

Postpartum mothers were recruited from the postnatal wards of two public hospitals in Hong Kong from 16 February to 30 July 2021. Participants were randomly assigned to either the control group or one of two intervention groups. Participants in the control group received standard publicly available information about rotavirus infection from the Centre for Health Protection by post within 3 to 5 days. Participants in intervention group 1 received the standard information and additionally an information sheet containing (1) key information about rotavirus risks for children and the benefits of vaccination, (2) eligible age for rotavirus vaccination, (3) a hyperlink to a government webpage listing private clinics that offer rotavirus vaccines, and (4) guidance on locating these clinics. A vaccination reminder text message containing the same hyperlink to the list of private clinics was sent when the child reached 6 to 8 weeks of age. Participants in intervention group 2 received all materials provided to intervention group 1 and additionally (1) contact details of a specific community health centre within the United Christian Nethersole Community Health Service located near their home and (2) a voucher for free rotavirus vaccination at the specified clinic.

An intention-to-treat analysis was used. Any missing rotavirus vaccination data were assumed to be non-vaccination. The effectiveness of the interventions in terms of increasing rotavirus vaccine uptake between groups was assessed using Chi-squared tests. Relative risks with 95% confidence intervals were calculated to determine the likelihood of vaccination across groups. Maternal attitudes were assessed postnatally and when children were approximately 8 months of age; paired differences were analysed using permutation tests.

Results

Of 1129 eligible mothers, 788 (70%) were randomly assigned to the control group (n=263), intervention group 1 (n=263), or intervention group 2 (n=262). In

these three groups, 48%, 56%, and 81% of children received rotavirus vaccines, respectively. The provision of key information about rotavirus and vaccination reminders increased rotavirus vaccine uptake by 1.17-fold or 8 percentage points (from 48% to 56%). Removal of financial barriers further increased uptake by 1.46-fold or 25 percentage points (from 56% to 81%). Overall, the full intervention package increased rotavirus vaccine uptake by 1.7-fold or 33 percentage points (from 48% to 81%), regardless of mothers' initial plans concerning rotavirus vaccination during the immediate postpartum period. Mothers in the intervention group 2 perceived the voucher for free rotavirus vaccination as the most important intervention component influencing their vaccination decision.

Provision of key information about rotavirus and vaccination reminders substantially increased uptake in the lower-income group (Table). The main reasons cited for not vaccinating their children were that the vaccine is excluded from the Childhood Immunisation Programme (according to mothers in intervention group 1 and the control group) and that knowledge of the vaccine is inadequate (according to mothers in intervention group 2) [Fig]. The intervention packages also strengthened mothers' confidence in decision to vaccinate their children.

Discussion

The intervention package effectively increased rotavirus vaccine uptake among Hong Kong children. Removal of the financial barrier was the most important component for increasing rotavirus vaccine uptake. The vaccine prevents hospitalisation in 92% to 96% of cases, and removal of the financial barrier could reduce rotavirus-related hospitalisation incidence by 23% to 24%.[1] Rotavirus vaccination also is cost-saving.[2] If incorporated into Hong Kong's Childhood Immunisation Programme, rotavirus vaccine uptake is likely to reach 95%,[3] potentially reducing rotavirus-related hospitalisation incidence by 57% to 60%. Further studies are needed to determine whether this intervention would be cost-effective if incorporated into routine public antenatal care.

Provision of key information and vaccination reminders substantially increased vaccine uptake in lower-income families. In Hong Kong, mothers from lower-income households tend to perceive less benefit from the rotavirus vaccine and have lower self-efficacy regarding vaccination, and thus are less likely to vaccinate their children against rotavirus.[4] Our intervention package may increase rotavirus vaccine uptake in this group by enhancing mothers' perceptions of the vaccine's benefits and their self-efficacy.

The increase in rotavirus vaccine uptake (ie, the effect of the intervention package) was smallest among families with a monthly household income of HK$30 000-39 999.

This study had some limitations. First, mothers were recruited from two public hospitals only. Mothers giving birth at private hospitals likely have higher household incomes and greater access to rotavirus vaccine information. However, 63% of Hong Kong births in 2021 occurred in public hospitals.[5] Second, demographic differences between mothers who declined and agreed to participate may have affected the representativeness of the sample. Mothers who declined were older and had lower education levels, and fewer had heard of rotavirus vaccine during the immediate postpartum period, compared with mothers who agreed to participate (56% vs 68%). Third, more mothers in the control group and intervention group 1 had missing rotavirus vaccination data, compared with intervention group 2. Missing vaccination data were regarded as non-vaccination, and additional analyses of intervention effectiveness were performed to include only those with documented vaccination status. Fourth, 33% of mothers in the control group reported that their vaccination decision had been influenced by study participation. Therefore, involvement in the study alone, without any intervention, may have affected their decision. Fifth, 6.7% of mothers in the intervention groups could not be contacted and may not have reviewed the additional information provided. For a conservative outcome, our intention-to-treat analysis assumed that all mothers in the intervention groups received the intervention.

TABLE. Rotavirus vaccine uptake by monthly household income across groups

Monthly household income, HK$	Uptake %			Difference in uptake, percentage points		
	Control	Intervention 1	Intervention 2	Intervention 1 vs control	Intervention 2 vs intervention 1	Intervention 2 vs control
<30 000	23	42	75	19	32	52
30 000-39 999	59	62	75	3	13	16
40 000-49 999	51	57	80	5	24	29
≥50 000	59	66	89	6	23	29

Conclusions

Provision of key information about rotavirus, vaccination reminders, and a voucher for free vaccination increased rotavirus vaccine uptake by 1.7-fold or 33 percentage points (from 48% to 81%). The intervention package enhanced mothers' confidence in decision to vaccinate their children. The intervention package was most effective among low-income families. This indicates that with removal of financial barriers, incorporation of the rotavirus vaccine into the Childhood Immunisation Programme could promote vaccine uptake equity and protect additional young children from rotavirus infection.

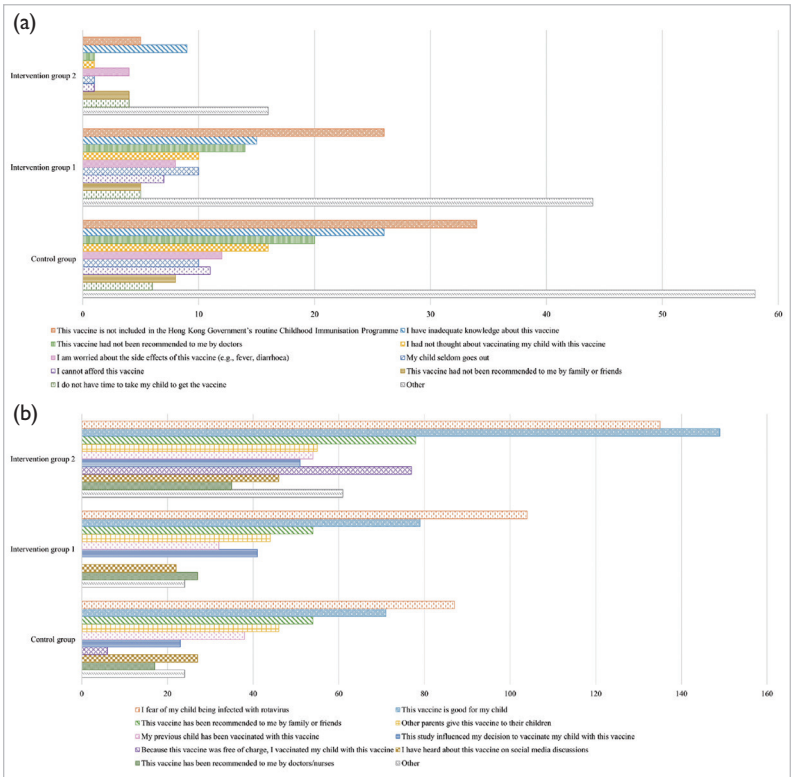


FIG. Mothers' perceived reasons for (a) not vaccinating and (b) vaccinating their children against rotavirus

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#19180202). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Yeung KHT, Yeung CCW, Tam WH, Liu KS, Fung GPG, Nelson EAS. Multiple-component interventions to increase rotavirus vaccine uptake in children: a randomised controlled trial. Lancet Reg Health West Pac 2024;50:101153.

Acknowledgements

We thank Kingson Liu for assistance with recruitment at United Christian Hospital; Joyce Tang, Ruby Lai, and the staff from the Christian Nethersole Community Health Service Preventive Medicine and Clinical Services Department for their support; Micky Tsz for conducting the pilot study; and the research staff for performing recruitment, delivering the intervention, and conducting interviews.

References

1. Yeung KHT, Tate JE, Chan CC, et al. Rotavirus vaccine effectiveness in Hong Kong children. Vaccine 2016;34:4935-42.
2. Yeung KHT, Lin SL, Clark A, et al. Economic evaluation of the introduction of rotavirus vaccine in Hong Kong. Vaccine 2021;39:45-58.
3. Shing S, Lui L, Ho B, Chen H. Control of multi-drug resistant organisms (MDROs) in residential care homes of elderly. Communicable Diseases Watch. Accessed 23 October 2024. Available from: https://www.chp.gov.hk/files/pdf/cdw_v19_6.pdf.
4. Yeung KHT. Identifying and lowering barriers to optimise interventions for pneumonia and diarrhoea in children. Accessed 7 November 2019. Available from: http://repository.lib.cuhk.edu.hk/en/item/cuhk-1839341.
5. Baby Friendly Hospital Initiative Hong Kong Association. World Breastfeeding Week (WBW) 1-7 August 2022. Accessed 3 October 2023. Available from: https://www.babyfriendly.org/hk/wp-content/uploads/2022/07/2022-WBW-Annual-Survey_E pdf 2022.

Lifestyle intervention using a mobile application versus booklet for adults with metabolic syndrome: a multicentre randomised controlled trial (abridged secondary publication)

DYP Leung *, EML Wong †, AMY Leung, ASP Cheung, KC Cheung

KEY MESSAGES

1. Compared with usual care, lifestyle intervention using educational support via the MetS app or booklet led to significantly greater reductions in body weight, waist circumference, body mass index, and systolic blood pressure, as well as increased total exercise time and amount, within 24 weeks.
2. Educational support via the MetS app was superior to that via a booklet for lifestyle intervention.
3. The Health Belief Model serves as an effective framework for designing intervention programmes for exercise initiation and adherence in patients with metabolic syndrome.

Hong Kong Med J 2024;30(Suppl 7):S12-6
HMRF project number: 16172411

[1] DYP Leung, [2] EML Wong, [1] AMY Leung, [2] ASP Cheung, [2] KC Cheung

[1] *School of Nursing, the Hong Kong Polytechnic University, Hong Kong SAR, China*
[2] *School of Nursing, Tung Wah College, Hong Kong SAR, China*

* Principal applicant: doris.yp.leung@polyu.edu.hk
† Corresponding author: elizawong@twc.edu.hk

Introduction

Metabolic syndrome—characterised by abdominal obesity, insulin resistance, hypertension, and hyperlipidaemia—is associated with elevated risks of diabetes, prediabetes, and cardiovascular disease.[1] E-health technology through mobile phones provides an effective means for delivering educational interventions to support patients with diabetes or metabolic syndrome.[2] The effects of e-health interventions compared with usual care or booklet-based approaches are usually reported separately.[3]

Considering the advantages of e-health programmes for patients with cardiometabolic diseases and the widespread smartphone usage among adults in Hong Kong,[1,2] we incorporated a custom-designed mobile application into an existing lifestyle intervention programme for patients with metabolic syndrome. This study aimed to compare health-related outcomes over 24 weeks among Hong Kong community adults with metabolic syndrome who received a health education programme using the MetS app, a booklet, or usual care.

Methods

This assessor-blinded, randomised controlled trial was conducted between August 2019 and December 2021. Chinese patients with metabolic syndrome who owned a smartphone and could read Chinese were recruited at two community centres in Hong Kong. Patients with physical, mental, visual, or cognitive impairments, or patients receiving prescribed medication for weight reduction were excluded.

Participants were randomly assigned to the app group, booklet group, or control group. All participants attended a 30-minute health talk related to metabolic syndrome care. Participants in the app group had the MetS app installed on their smartphones to view educational content. Additionally, a membership area within the app provided individual support for self-health monitoring, goal setting for exercise plans, and exercise tracking. The membership area and interactive platform enabled participants to self-monitor exercise, body weight, and waist circumference, thereby enhancing self-efficacy for exercise initiation, self-monitoring, and adherence. The design of the app was guided by the Health Belief Model.[4] These participants received one automated health message each day. Participants in the booklet group received a lifestyle intervention booklet, which included information about metabolic syndrome and advice on diet, exercise, medication, lifestyle, and stress management.[3] Participants in the control group were advised to maintain their usual activities; they received a placebo leaflet containing health information about obesity and a healthy lifestyle.

Outcome measures included body weight, total exercise time and amount, improvement in any two cardiometabolic risk factors (waist circumference, body mass index, systolic blood pressure, high-density lipoprotein cholesterol, triglycerides, and blood glucose level), cardiovascular endurance,

exercise self-efficacy, and stress level. Outcomes were assessed at baseline, 4 weeks, 12 weeks, and 24 weeks.

All tests were two-sided, and a P value of <0.05 was considered statistically significant. The intention-to-treat principle was applied. Generalised estimating equation models, adjusted for any confounders, were used to compare changes in outcomes over time between groups.

Results

Of 368 patients screened, 264 (71.7%) completed the baseline assessment and were randomly assigned to the app group (n=88), booklet group (n=88), or control group (n=88). The dropout rates were 8%, 6.8%, and 4.8%, respectively. The three groups were comparable in terms of baseline characteristics, except for sex, education level, and marital status (Table 1). Generalised estimating equation analyses were adjusted for the effects of these three variables on study outcomes.

Compared with the control group, the app group showed greater reductions in body weight, with the reductions increasing over time, whereas the booklet group displayed no significant difference in body weight reduction across the three time points (Table 2). Similarly, the app group achieved a

TABLE 1. Baseline characteristics of participants (n=264)

Variable	App group (n=88)*	Booklet group (n=88)*	Control group (n=88)*	P value
Sex				0.002
Male	35 (39.8)	18 (20.5)	16 (18.2)	
Female	53 (60.2)	70 (79.5)	72 (81.8)	
Age, y	61.59±10.30	62.10±8.29	63.56±12.73	0.444
Education level				<0.001
Primary school/no formal education	13 (14.8)	11 (12.5)	31 (35.2)	
Secondary school	42 (47.7)	61 (69.3)	38 (43.2)	
Tertiary education	33 (37.5)	16 (18.2)	19 (21.6)	
Marital status				0.043
Married	64 (72.7)	48 (54.5)	55 (62.5)	
Unmarried/widowed/divorced/separated	24 (27.3)	40 (45.5)	33 (37.5)	
Employment				0.479
Full-time job	22 (25.0)	21 (23.9)	26 (29.5)	
Part-time job	9 (10.2)	9 (10.2)	9 (10.2)	
Housewife	12 (13.6)	17 (19.3)	21 (23.9)	
Retired/others	45 (51.1)	41 (46.6)	32 (36.4)	
Financial status				0.094
Good	23 (26.1)	13 (14.8)	17 (19.3)	
Average	56 (63.6)	66 (75.0)	54 (61.4)	
Poor	9 (10.2)	9 (10.2)	17 (19.3)	
Residential status				0.112
Live alone	10 (11.4)	21 (23.9)	20 (22.7)	
Live with family	78 (88.6)	67 (76.1)	68 (77.3)	
Exercise				0.784
Regularly	51 (58.0)	44 (50.0)	46 (52.3)	
Sometimes	33 (37.5)	38 (43.2)	35 (39.8)	
No	4 (4.5)	6 (6.8)	7 (8.0)	
Smoking				0.238
Current smoker	1 (1.1)	0	4 (4.5)	
Former smoker	7 (8.0)	8 (9.1)	6 (6.8)	
Never smoker	80 (90.9)	80 (90.9)	78 (88.6)	

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

TABLE 2. Comparisons of outcomes among the app, booklet, and control groups across three time points

Outcome	App and booklet vs control*	P value	App vs booklet*	P value
Body weight, kg				
App group				
Week 4	-0.351 (-0.655 to -0.047)	0.024	-0.400 (-1.000 to 0.201)	0.192
Week 12	-1.044 (-1.613 to -0.476)	<0.001	-0.674 (-1.374 to 0.025)	0.059
Week 24	-1.710 (-2.423 to -0.998)	<0.001	-1.244 (-2.041 to -0.446)	0.002
Booklet group				
Week 4	0.055 (-0.522 to 0.631)	0.853	-	-
Week 12	-0.352 (-1.005 to 0.301)	0.291	-	-
Week 24	-0.435 (-1.126 to 0.257)	0.218	-	-
Total exercise time and amount				
App group				
Week 4	7.511 (1.528 to 13.493)	0.014	8.337 (0.545 to 16.128)	0.036
Week 12	11.315 (5.353 to 17.278)	<0.001	4.467 (-2.509 to 11.443)	0.209
Week 24	11.950 (5.486 to 18.414)	<0.001	11.621 (5.146 to 18.095)	<0.001
Booklet group				
Week 4	-0.768 (-8.208 to 6.672)	0.840	-	-
Week 12	6.926 (-0.632 to 13.219)	0.031	-	-
Week 24	0.387 (-5.006 to 5.780)	0.888	-	-
Waist circumference, cm				
App group				
Week 12	-3.458 (-4.898 to -2.017)	<0.001	-1.186 (-2.484 to 0.112)	0.073
Week 24	-4.696 (-5.927 to -3.466)	<0.001	-2.731 (-4.091 to -1.371)	<0.001
Booklet group				
Week 12	-2.287 (-3.827 to -0.747)	0.004	-	-
Week 24	-1.954 (-3.256 to -0.651)	0.003	-	-
Body mass index				
App group				
Week 4	-0.263 (-0.525 to 2.921)	0.050	-0.153 (-0.376 to 0.071)	0.181
Week 12	-0.494 (-0.805 to -0.183)	0.002	-0.250 (-0.512 to 0.013)	0.062
Week 24	-0.799 (-1.152 to -0.445)	<0.001	-0.477 (-0.777 to -0.176)	0.002
Booklet group				
Week 4	-0.109 (-0.427 to 0.208)	0.499	-	-
Week 12	-0.242 (-0.573 to 0.089)	0.151	-	-
Week 24	-0.318 (-0.661 to 0.025)	0.069	-	-
Systolic blood pressure				
App group				
Week 12	-4.122 (-8.112 to -0.133)	0.043	-1.520 (-5.445 to 2.406)	0.448
Week 24	-2.442 (-7.001 to 2.118)	0.294	-4.919 (-9.260 to -0.578)	0.026
Booklet group				
Week 12	-2.615 (-6.841 to 1.611)	0.225	-	-
Week 24	2.468 (-2.073 to 7.009)	0.287	-	-
Diastolic blood pressure				
App group				
Week 12	-1.766 (-4.190 to 0.659)	0.153	0.005 (-2.255 to 2.265)	0.996
Week 24	-1.520 (-3.904 to 0.865)	0.212	-1.686 (-4.201 to 0.829)	0.189
Booklet group				
Week 12	-1.719 (-4.037 to 0.599)	0.146	-	-
Week 24	0.213 (-2.250 to 2.677)	0.865	-	-

* Data are presented as beta coefficient (95% confidence interval)

TABLE 2. (cont'd)

Outcome	App and booklet vs control*	P value	App vs booklet*	P value
High-density lipoprotein cholesterol				
App group				
Week 12	-0.007 (-0.074 to 0.059)	0.831	0.049 (-0.017 to 0.114)	0.146
Week 24	-0.055 (-0.129 to 0.019)	0.147	-	-
Triglycerides				
App group				
Week 12	0.009 (-0.327 to 0.345)	0.957	-0.179 (-0.508 to 0.228)	0.397
Week 24	0.191 (-0.108 to 0.490)	0.210	-	-
Fasting blood glucose				
App group				
Week 12	0.100 (-0.154 to 0.354)	0.441	-0.041 (-0.248 to 0.165)	0.694
Week 24	0.276 (-0.001 to 0.553)	0.051	0.030 (-0.176 to 0.235)	0.777
Booklet group				
Week 12	0.141 (-0.119 to 0.401)	0.289	-	-
Week 24	0.245 (-0.043 to 0.533)	0.095	-	-
3-mins step test				
App group				
Week 12	0.107 (-0.342 to 0.557)	0.640	0.098 (-0.423 to 0.620)	0.711
Week 24	0.048 (-0.424 to 0.519)	0.843	-0.057 (-0.579 to 0.466)	0.832
Booklet group				
Week 12	0.008 (-0.491 to 0.507)	0.976	-	-
Week 24	0.100 (-0.389 to 0.590)	0.688	-	-
Self-efficacy for exercise				
App group				
Week 4	0.259 (-0.278 to 0.795)	0.345	0.062 (-0.522 to 0.646)	0.836
Week 12	0.557 (-0.096 to 1.210)	0.095	0.042 (-0.574 to 0.657)	0.894
Week 24	0.408 (-0.287 to 1.102)	0.250	0.266 (-0.361 to 0.892)	0.406
Booklet group				
Week 4	0.203 (-0.467 to 0.874)	0.552	-	-
Week 12	0.536 (-0.209 to 1.280)	0.158	-	-
Week 24	0.241 (-0.498 to 0.981)	0.522	-	-
Perceived stress scale				
App group				
Week 4	-0.579 (-1.810 to 0.652)	0.357	-0.291 (-1.590 to 1.008)	0.661
Week 12	-0.103 (-1.626 to 1.419)	0.894	0.484 (-0.940 to 1.909)	0.505
Week 24	-0.319 (-2.382 to 1.744)	0.762	-0.215 (-1.927 to 1.498)	0.806
Booklet group				
Week 4	-0.285 (-1.525 to 0.954)	0.652	-	-
Week 12	-0.594 (-2.036 to 0.848)	0.420	-	-
Week 24	-0.111 (-2.055 to 1.834)	0.911	-	-

greater increase in exercise time at each time point. Regarding cardiometabolic risk factors, both the app and booklet groups exhibited significant reductions in waist circumference at weeks 12 and 24; effects were greater in the app group than in the booklet group. Compared with the control group, the app group also showed significant reductions in body mass index at weeks 12 and 24 and in systolic blood pressure at week 12. Compared with the control group, both the app and booklet groups had greater improvements in the cardiovascular endurance (as measured by the 3-min step test) and self-efficacy for exercise, and larger reductions in perceived stress at all three time points.

Compared with the booklet group, the app group showed greater reduction in body weight at week 24, increased total exercise time and amount at weeks 4 and 24, and reductions in waist circumference, body mass index, and systolic blood pressure at week 24.

Discussion

The lifestyle intervention programme via the MetS app was superior to that via a booklet in reducing body weight, body mass index, waist circumference, and systolic blood pressure, as well as increasing total exercise time and amount, within 24 weeks. These results suggest that the app effectively promoted regular aerobic exercise, leading to reductions in weight and central obesity. Our findings are consistent with the literature, which shows that a structured e-health programme with features to support self-monitoring, feedback, and goal setting can facilitate behavioural changes (eg, increased exercise frequency and duration).[5] The MetS app may have motivated participants to engage in dietary control, exercise initiation, and adherence, leading to greater total exercise time and amount and body weight reduction.[5]

Fluctuations in exercise self-efficacy were observed in the booklet and control groups, but exercise self-efficacy was significantly improved in the app group. These fluctuations might reflect the limited effect duration (4 weeks) of the nurse-led health talk at baseline. No significant improvements were observed for stress management, although a trend toward stress reduction was observed in the app and booklet groups.

Conclusion

The lifestyle intervention programme via the MetS app was superior to that via a booklet in reducing body weight, body mass index, waist circumference, and systolic blood pressure, as well as increasing exercise time and amount, within 24 weeks.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#16172411). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Wong EML, Tam HL, Leung AYM, Cheung ASP, Cheung KC, Leung DYP. Impacts of educational interventions with support of mobile app versus booklet for patients with hypertension and metabolic syndrome: a secondary data analysis. Int J Environ Res Public Health 2022;19:12591.
2. Wong EML, Leung DYP, Wang Q, Leung AYM, Cheung ASP. The effect of a lifestyle intervention program using a mobile application versus the effect of a program using a booklet for adults with metabolic syndrome: a three-arm randomized controlled trial. J Nurs Scholarsh 2023;55:936-48.

Acknowledgments

We thank Happy-Retired.com and the Institute of Active Aging, The Hong Kong Polytechnic University, for their support in promoting this programme.

References

1. International Diabetes Federation. Consensus statements: the IDF Consensus Worldwide Definition of the Metabolic Syndrome. Accessed 3 September 2022. Available from: https://idf.org/media/uploads/2023/05/attachments-30.pdf.
2. World Health Organization. Digital health. Accessed 3 September 2022. Available from: http://www.who.int/ehealth/en/
3. Wang Q, Chair SY, Wong EM. The effects of a lifestyle intervention program on physical outcomes, depression, and quality of life in adults with metabolic syndrome: a randomized clinical trial. Int J Cardiol 2016;230:461-7.
4. Janz N, Champion V, Strecher V. The health belief model. In: Glans K, Rimer B, Lewis F, editors. Health Behavior and Health Education – Theory, Research and Practice. 3rd ed. San Francisco: Jossey-Bass, John Wiley & Sons; 2002.
5. Whitehead L, Seaton P. The effectiveness of self-management mobile phone and tablet apps in long-term condition management: a systematic review. J Med Internet Res 2016;18:e97.

Family barriers and facilitators for healthy eating habits among adolescents: abridged secondary publication

CLK Lam *, KSN Liu, JY Chen, KS Sun, JPY Tsang, P Ip

KEY MESSAGES

1. Adolescents lack adequate knowledge of recommended quantities for specific food types, perceive low susceptibility to the harm from unhealthy eating, make unhealthy snacking and food choices in restaurants, and consume insufficient fruits and vegetables.
2. Positive parental attitudes towards healthy eating, provision of healthy foods at home, and parental supervision facilitate healthy eating in adolescents.
3. Family barriers to healthy eating habits include insufficient parental knowledge, time and cost concerns, and limited discussions about food within the family.
4. Strategies to improve healthy eating habits include incorporating healthy ingredients into adolescents' favourite recipes, providing a variety of fruits and vegetables at home, and involving adolescents in meal preparation.

Hong Kong Med J 2024;30(Suppl 7):S17-21
HMRF project number: 18191581

[1] CLK Lam, [1] KSN Liu, [1] JY Chen, [2] KS Sun, [1] JPY Tsang, [3] P Ip

[1] *Department of Family Medicine and Primary Care, The University of Hong Kong, Hong Kong SAR, China*
[2] *Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, China*
[3] *Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong SAR, China*

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

Introduction

Over 80% of adolescents in Hong Kong have unhealthy diets, which increase their risk of obesity and non-communicable diseases. Most adolescents in Hong Kong consume insufficient fruits and vegetables (FV) but excessive salt and sugar. It is important to understand adolescents' knowledge, attitudes, and practices (KAP) related to healthy eating. Family influences the home food environment of adolescents, which may in turn shape their KAP regarding healthy eating. Parental characteristics (illness experience, knowledge, attitudes, and socioeconomic factors) and food parenting practices (eg, food provision and parental supervision) can affect adolescents' eating habits.[1] This study aimed to explore dietary KAP among adolescents and the associated family facilitators, barriers, and strategies within Chinese families.

Methods

Families with adolescents aged 10 to 19 years who could speak Cantonese were recruited from participants of Trekkers Family Enhancement Scheme that evaluated the effectiveness of a health and social empowerment programme for low-income families.[2] Stratified purposive sampling was applied based on adolescents' daily consumption of FV, age, and sex, as well as household income and attendance at previous nutrition workshops.

Parent-adolescent dyads were interviewed on Zoom by an interviewer trained in qualitative research, with a trained research assistant as an observer. A semi-structured interview guide developed from the KAP framework was used. Questions were directed to the adolescents, and parents provided supplementary responses. Each interview lasted 30 to 60 minutes; data saturation was reached by the 25th interview.

Thematic analysis was conducted in accordance with a six-phase guide.[3] Interview recordings were transcribed verbatim in Chinese and analysed using the NVivo software. Two trained researchers independently coded the transcripts, and inconsistencies were resolved by the team. Adolescents' KAP were categorised into KAP in common and KAP gaps. Family factors were categorised into parental characteristics and food parenting practices.

Results

Of 138 families contacted, 25 agreed to participate (Table 1). Among the adolescents, eight (32%) reported consuming ≥5 servings of FV intake per day (ie, healthy intake). Twenty-one (84%) families had a monthly household income below the population median.

Twelve themes emerged from the interviews and were categorised under the constructs of

TABLE 1. Characteristics of participants (n=25)

Characteristic	Value*
Adolescents	
Sex	
Female	13 (52.0)
Male	12 (48.0)
Age, y	14.84±2.08
12-13	8 (32.0)
14-16	10 (40.0)
17-19	7 (28.0)
Fruit and vegetable intake per day	3.6±1.53
≥5 servings (healthy)	8 (32.0)
3-4 servings (average)	11 (44.0)
1-2 servings (unhealthy)	6 (24.0)
Parents	
Female sex	25 (100)
Age, y	49.24±4.65
40-49	14 (56.0)
50-59	11 (44.0)
Participation in nutrition workshop	10 (40.0)
Household monthly income, HK$	
>27 000	4 (16.0)
20 000-26 999	5 (20.0)
13 500-19 999	8 (32.0)
13 500	8 (32.0)

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

knowledge (n=4), attitude (n=3), and practice (n=5) [Table 2].

Regarding knowledge, adolescents understood the relative portions but not the recommended quantities for specific food categories. They focused on observable short-term health consequences of unhealthy eating, rather than long-term outcomes. Although they could distinguish between healthy and unhealthy foods based on nutritional content, they could not identify healthy snack options. They were aware of unhealthy cooking methods commonly used in restaurants but were unsure whether healthy menu options were available.

Regarding attitudes, the perceived necessity of healthy eating was primarily influenced by previous experiences with unhealthy eating. Some adolescents perceived a low susceptibility to the health consequences of unhealthy eating due to their young age and 'good' metabolism. Health was not always their top priority when competing with taste and convenience in food choices. Taste was the top priority, especially when eating out or snacking. Some adolescents described their self-efficacy in healthy eating by assessing changes in body shape and balancing diet with exercise; others lacked the necessary food preparation skills for FV.

Regarding practices, adolescents usually ate more balanced meals prepared by their parents at home but preferred less healthy, easy-to-cook options when cooking for themselves. Eating out or getting takeaway food was more common for lunch on school days. Food choices were often based on taste preferences for strong flavours and meat. They occasionally purchased snacks but seldom read nutrition labels, prioritising taste and convenience. Many adolescents consumed insufficient FV because dinner was often the only meal with FV included. Fruit consumption tended to be a family practice, prepared by parents after dinner; only a few adolescents served themselves fruit. Vegetable consumption when eating out was infrequent due to perceived low value for money, limited availability, and unhealthy cooking methods. Snacking was uncommon among adolescents from low-income families, but most snacks available at home were predominantly unhealthy.

Additionally, 14 themes were identified for family factors affecting healthy eating, categorised under parental characteristics (n=8) and food parenting practices (n=6) [Table 3].

Regarding parental characteristics, positive outcomes from healthy eating or chronic illnesses experienced by parents and other family members helped adolescents to develop positive attitudes towards healthy eating, as did parental knowledge of recommended food proportions in a meal and healthy cooking methods. Barriers included a lack of knowledge about the recommended servings and classification of FV, methods for preparing tasty and healthy meals, and alternatives to salty seasonings. Many parents recognised the importance of healthy eating for health but did not practise it for eating out or snacking due to a lack of knowledge about healthy options available. Parents often stocked unhealthy, easy-to-cook foods at home for adolescents to cook for themselves. Lack of time was also a barrier; parents needed to balance between household chores and work, and adolescents often eat out or select takeaway food. Concerns about cost limited eating out and snacking in many families; they often avoided stocking fresh FV, preferring frozen or ready-to-cook meat over more expensive fresh meat.

Regarding food parenting practices, some parents provided nutrition education to their adolescents, which facilitated the latter's dietary knowledge. However, discussions of food-related matters among family members were uncommon. Parents felt it was unnecessary because they believed their eating habits were already healthy. Parental role modelling of healthy eating was perceived as

TABLE 2. Summary of themes for adolescents' knowledge, attitudes, and practices (KAP) related to healthy eating

KAP in common	KAP gaps	
	Insufficiency	Inaccuracy/unhealthy
Knowledge		
1. Dietary recommendations		
• Relative portions of food categories (eg, food pyramid, low sugar, oil, salt)	• Recommended daily servings or allowances (eg, 3-2-1 lunchbox portion, salt content in noodle soup)	• Underestimating recommended servings (eg, one apple daily)
2. Health outcomes of healthy eating		
• Observable short-term outcomes (eg, constipation, body weight, skincare, sore throat)	• Specific benefits of eating fruits and vegetables (eg, reduced body pain, improved skincare, detoxification) • Long-term outcomes (eg, cardiovascular disease, cancer)	
3. Nutrition content in food		
• Food sources of fat, salt, and sugar (eg, seasonings, salty snacks) • Food sources of nutrients (eg, protein, calcium) • Interpretation of nutrition labels or claims	• Healthy snack options (eg, yogurt, fruit, nuts)	
4. Access to healthy meals		
• Unhealthy cooking methods used in restaurant and takeaway food	• Ways to identify healthier menu choices in restaurants	
Attitudes		
5. Outcome expectations for healthy eating		
• Experience of negative outcomes from unhealthy eating habits	• Experience of positive outcomes from healthy eating habits	• Belief that healthy eating is only necessary for older adults and not for young people
6. Food preferences		
• Taste preference for unhealthy food	• Prioritising taste and convenience more than health	• Perceived inferior taste of healthy food
7. Self-efficacy for healthy eating		
• Assessing health by body shape and balancing diet and exercise	• Strategies for healthy eating with friends or on their own • Food preparation skills	
Practices		
8. Grocery shopping for healthy food		
• No habit of reading nutrition labels or health claims	• Reading nutrition labels to identify healthy alternatives • Accompanying parents when grocery shopping	
9. Eating home-prepared meals		
• Meals prepared by parents • Consuming ready-to-eat or easy-to-cook food for breakfast • Eating grains, vegetables, and meat for lunch and/or dinner		• Use of unhealthy ingredients when preparing food for themselves
10. Eating out in restaurants or takeaway food		
• Eating out or buying takeaway for lunch after school	• Infrequent eating out with family or friends	• Availability of unhealthy eating-out options • Occasional purchase of unhealthy takeaway food for family meals

the family norm by adolescents, which facilitated their acceptance and preference for these practices. However, the parental practice of not eating fruit daily was a barrier to healthy eating habits in adolescents. Controlling food provision at home including home-prepared meals, various FV, and snacks was practised by many parents to facilitate their adolescents' acceptance of healthy food and reduce their desire for unhealthy snacks. Involving adolescents in food-related tasks was an effective strategy to empower them to make healthy food choices and prepare healthy meals. This may not be feasible in some families where working parents lack time to supervise cooking by adolescents or children

TABLE 3. Influence of parental characteristics and food parenting practices on adolescents' knowledge, attitudes and practices related to healthy eating

Themes	Family factors		Influence on adolescents*		
	Facilitators	Barriers	Knowledge	Attitudes	Practices
Family health					
1. Illness experience in the family	Witnessing positive health outcomes of healthy eating		+	+	
	Perceived risk of health problems			+	+
Parental knowledge					
2. Dietary recommendations	Ensuring vegetable intake in daily meals	Uncertain about recommended servings and definitions of fruits and vegetables	-	-	+/-
3. Preparation of healthy food	Healthy cooking methods and varied presentations of vegetables	Lack of knowledge about making tasty food that is low in oil and seasonings	+	+/-	+/-
	Balancing health with taste of adolescents in cooking	Lack of knowledge about healthy alternatives to salty seasonings		+	+/-
	Homemade drinks to replace prepackaged beverages				+
4. Healthy food choices		Lack of knowledge about healthy options when eating out			-
		Unhealthy instant food for adolescents to cook for themselves			-
Parental attitudes					
5. Importance of healthy eating	Belief in the impact of eating habits on own and adolescents' health		+	+	+
6. Priority of family health	Consideration of health in food choices	Prioritising taste over health when eating out or snacking		+	+/-
Socioeconomic factors					
7. Time concerns		Lack of time for home cooking			-
		Convenience of eating out or purchasing takeaway food			-
		Prioritising adolescent school schedules over healthy eating habits			-
8. Cost concerns	Saving money by limiting eating out and snacking	Choosing frozen or ready-to-cook meat for lower cost			+/-
		Concern about food waste limits the stocking of fresh fruit at home			-
Food parenting practices					
9. Nutrition education	Education on health outcomes of eating habits	Limited discussion of food-related issues within the family	+/-		
	Education on healthy eating-out options		+		
10. Role modelling	Parental practices of healthy eating	Parents lacking a habit of daily fruit consumption		+/-	+/-
11. Food provision	Regular home-prepared meals			+	+
	Various fruits and vegetables at home	Unhealthy snacks at home		+/-	+/-
	Ready-to-eat fruits				+
12. Child involvement	Joint decision-making about healthy food choices during grocery shopping	Parents with little time to supervise meal preparation by adolescents	+/-		
	Involving adolescents in food preparation	Adolescents with no responsibility for food preparation	+/-		+
	Ready-to-cook food available for adolescents				+
13. Parental supervision	Monitoring and prompting food consumption	Lack of control over or supervision of adolescents' eating habits	+/-	+	+/-
	Setting food rules and explaining expectations		+		+
14. Cultivation of food preference	Highlighting positive attributes of fruits and vegetables (eg, taste and fun)			+	+
	Considering adolescents' preferences when preparing home meals, fruits, and vegetables			+	+

* '+' denotes effect of facilitator, and '-' denotes effect of barrier

were exempted from food-related responsibilities. Monitoring, reminders, and rules facilitated healthy eating habits among adolescents. Nonetheless, the belief that their adolescents were old enough to make their own food decisions, especially regarding snacking, was an unintentional barrier. Parents reported strategies such as highlighting the positive attributes of healthy food and considering their adolescents' food preferences during meal preparation could cultivate healthy food practices.

Discussion

Adolescents had general knowledge of healthy eating and perceived its importance for short-term health outcomes. Most reported a lower frequency of eating out and snacking compared with Asian adolescents in a previous study.[4] The lower household incomes (and thus smaller food budgets) of our participants may partly explain this difference.

A lack of knowledge about the recommended quantities of specific food types could lead to non-adherence to dietary recommendations. The uncommon inclusion of healthy snacks such as nuts, corn, and raw vegetables in the traditional Chinese diet, along with a lack of awareness of healthier options available in restaurants, form barriers to adopting healthy snacking and eating-out practices.

Many adolescents perceived a low susceptibility to the potential harms of unhealthy eating and were unaware of the cumulative metabolic risks associated with it. They were unwilling to prioritise health over taste, convenience, and cost. Emphases on the immediate and visible health benefits of healthy eating may be more effective efforts to engage adolescents.

Adolescents in Chinese families often have limited responsibility in home meal preparing and thus lack skills to cook healthy meals for themselves. Insufficient FV intake is partly related to the Chinese practice of eating cooked vegetables and serving fruit at the end of a meal, and partly due to the inconvenience of preparation. Serving FV on more occasions and making ready-to-eat FV more available may facilitate sufficient intake.

Key family facilitators included positive parental attitudes towards healthy eating, provision of healthy food, and parental supervision. Main barriers were deficiencies in parental dietary knowledge, time and cost concerns, and limited family discussions of food-related matters. A knowledge deficit in dietary recommendations appears common among adults across Eastern and Western regions. Time and cost concerns were the main family barriers to healthy eating practices among adolescents, consistent with findings from a previous study.[5] Some parents tended to prioritise cost and convenience over health in food decisions, which unintentionally led to similar attitudes in their adolescents. Regular family discussions of food-related matters could increase adolescents' awareness of healthy eating.

Families reported strategies to improve healthy eating habits among adolescents such as incorporating healthy ingredients into adolescents' favourite recipes, providing a variety of FV at home, and involving adolescents in meal preparation. These strategies demonstrated an authoritative parenting style that combines regulation with consideration of adolescents' food preferences in meal preparing, home food environment, and cooking skills education. Such approaches may also increase adolescents' self-efficacy to healthy eating.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#18191581). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Liu KSN, Chen JY, Sun KS, Tsang JPY, Ip P, Lam CLK. Family facilitators of, barriers to and strategies for healthy eating among Chinese adolescents: qualitative interviews with parent–adolescent dyads. Nutrients 2023;15:651.
2. Liu KSN, Chen JY, Sun KS, Tsang JPY, Ip P, Lam CLK. Adolescent knowledge, attitudes and practices of healthy eating: findings of qualitative interviews among Hong Kong families. Nutrients 2022;14:2857.

Acknowledgements

We thank Kerry Group Kuok Foundation (Hong Kong) Limited for establishing the Trekkers Family Enhancement Scheme.

References

1. Vaughn AE, Ward DS, Fisher JO, et al. Fundamental constructs in food parenting practices: a content map to guide future research. Nutr Rev 2016;74:98-117.
2. Fung CS, Yu EY, Guo VY, et al. Development of a health empowerment programme to improve the health of working poor families: protocol for a prospective cohort study in Hong Kong. BMJ Open 2016;6:e010015.
3. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77-101.
4. Lim HS, Kim TH, Lee HH, et al. Fast food consumption alongside socioeconomic status, stress, exercise, and sleep duration are associated with menstrual irregularities in Korean adolescents: Korea National Health and Nutrition Examination Survey 2009-2013. Asia Pac J Clin Nutr 2018;27:1146-54.
5. Darmon N, Drewnowski A. Does social class predict diet quality? Am J Clin Nutr 2008;87:1107-17.

Peer-led self-management programme for people with recent-onset psychosis: a randomised controlled trial (abridged secondary publication)

WT Chien *, D Bressington, R Gray, SY Chan, DI Lubman

KEY MESSAGES

1. The peer-led self-management intervention (PLSMI), in addition to usual care, is an effective intervention for people with recent-onset psychosis. It significantly improves patients' recovery during long-term follow-up.
2. The PLSMI results in significantly greater improvements in patients' functioning, symptoms, illness insight, re-hospitalisation rates, and service satisfaction over an 18-month follow-up period, compared with psychoeducation or usual care alone.
3. Participants perceive that the PLSMI enhances their hope for recovery and social support, while improving their self-care skills and functioning in daily living.

Hong Kong Med J 2024;30(Suppl 7):S22-7
HMRF project number: 17180291

[1] **WT Chien**, [2] **D Bressington**, [3] **R Gray**, [4] **SY Chan**, [5] **DI Lubman**

[1] *Nethersole School of Nursing, Faculty of Medicine, The Chinese University of Hong Kong SAR, China*
[2] *School of Nursing, The Hong Kong Polytechnic University, Hong Kong SAR, China*
[3] *School of Nursing and Midwifery, La Trobe University, Melbourne, Australia*
[4] *Caritas Integrated Family Services, Caritas Hong Kong, Hong Kong SAR, China*
[5] *Clinical Health School, Monash University, Melbourne, Australia*

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

Introduction

Psychosis affects more than 30% of psychiatric patients worldwide and is associated with a high risk of relapse in the early stages of illness. Psychosocial interventions can improve symptoms and reduce relapses, but evidence concerning psychosocial health and functional outcomes remains inconsistent and inconclusive.[1] Recovery-focused interventions maximise self-care and problem-solving for illness management and may better meet service users' needs. Additionally, peer support workers who have recovered from psychosis serve as role models, encouraging active and autonomous recovery in peers and co-patients. This multicentre, three-arm, randomised controlled trial aimed to evaluate the effectiveness of the peer support worker–led self-management intervention (PLSMI) over 18 months in patients with recent-onset psychosis, compared with a psychoeducation (PE) group and a treatment-as-usual (TAU) group. Perceived benefits and limitations of the intervention were examined from participants' and interveners' perspectives.

Methods

Chinese patients aged 18 to 60 years with a recent-onset (≤3 years) psychotic disorder (based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria) attending one of six Integrated Community Centres for Mental Wellness in Hong Kong who had a Global Assessment of Functioning score of ≥51 and were mentally stable to receive intervention were assessed for eligibility. Patients were excluded if they had recently received psychoeducation or psychotherapy, visual, language, or communication difficulties, or a history of serious mental or medical diseases.

Assuming a 5% significance level and a 15% attrition rate, we aimed to recruit 180 participants (60 per group) to detect a medium effect size on recovery (Cohen's d=0.52) with 80% power.[2] The TAU group received standard community mental healthcare services. The PLSMI group (divided into five subgroups with 12 to 14 participants each) received community services in addition to ten 1.5-hour sessions, held weekly or biweekly, led by a peer support worker based on the crisis-resolution-team optimisation and relapse prevention programme.[3] The PE group (also divided into five subgroups) received community services and intervention sessions led by an advanced nurse based on psychoeducation programmes for psychosis.[4]

Outcome measures included the Questionnaire about the Process of Recovery (for progress of recovery), the Insight and Treatment Attitude Questionnaire (for insight into illness and treatment), the Specific Level of Functioning Scale (for functioning), the Positive and Negative Syndrome Scale (for mental state), the Revised Social-Problem-Solving Inventory (for problem-solving ability), the Client Satisfaction Questionnaire (for service satisfaction), and re-hospitalisation rates. Participants were assessed at baseline, 1 week, 6 months, 12 months, and 18 months.

A purposive sample of approximately 15 participants (including similar proportions of individuals with very positive, negative, and minimal score changes in recovery and functioning) was recruited for four focus-group interviews (three for PLSMI participants and one for peer support workers) after completing T1 to identify perceived strengths and limitations of the PLSMI.

The homogeneity of study groups was examined, and analyses were performed based on the intention-to-treat principle. Generalised estimating equation tests were conducted, followed by pairwise contrast tests. Missing data were estimated using maximum likelihood estimation, followed by repeated-measures analysis of variance and Helmert contrasts tests. No covariance analysis was performed because no significant differences were observed between groups at baseline. The time to hospitalisation over the 18-month follow-up was analysed using survival analysis and the Cox regression test. Differences among centres and between completers (>6 sessions) and non-completers (≤4 sessions) in the PLSMI were examined using the Kruskal-Wallis test. A P value of <0.05 was considered statistically significant. Content analysis was conducted on focus-group interview data.

Results

Of 560 eligible patients, 480 (85.7%) agreed to participate. Among these, 180 participants (30 per centre) were randomly selected and assigned to the PLSMI, PE, or TAU group. Of the 180 participants, 171 who completed the intervention (>6 group sessions) and follow-up were included in the analysis. The mean numbers of attendances at PLSMI and PE group sessions were 8.6±1.0 (range, 4-10) and 8.1±1.2 (range, 3-10), respectively. The three groups were comparable in terms of baseline characteristics (Table 1).

Significant group × time effects were observed for six outcomes over 18 months (Wald's χ^2=13.40-25.48, P=0.01-0.001), with moderate to large effect sizes (η^2=0.13-0.23) [Table 2]. Compared with the TAU group, the PLSMI group showed greater improvements from 1 week to 18 months in terms of recovery, functioning, psychotic symptoms, and duration of re-hospitalisations, as well as from 6 to 18 months in terms of insight into treatment/illness and service satisfaction. Compared with the PE group, the PLSMI group demonstrated greater improvements at 12 and/or 18 months in terms of psychotic symptoms, insight into treatment/illness, service satisfaction, and duration of re-hospitalisations.

Compared with the TAU group, the PLSMI group had a longer time to hospitalisation (90.85 vs 48.92 days). Kaplan-Meier survival curves indicated that survival rates (no hospitalisation) were significantly higher in the PLSMI group than in the TAU group at 6 months (81.03% vs 44.64%, P=0.003), 12 months (77.58% vs 41.07%, P=0.003), and 18 months (74.13% vs 19.65%, P=0.001). No significant differences were found among study centres or between completers and non-completers in the PLSMI group.

Focus-group interviews revealed four perceived benefits (enhanced hope for recovery, increased social support, better self-care skills, and improved functioning) and three limitations (concerns about instability or increased severity of psychotic symptoms, concerns about the need for very long-term treatment, and challenges in self-care or problem-solving in daily life) of the PLSMI. Most PLSMI participants expressed that although they understood the treatment and recovery process could be a long-term 'battle' requiring sustained self-care and illness management, they could maintain hope for recovery and improved self-care and functioning, with satisfactory support from peers and health professionals.

Discussion

The 4-month PLSMI for people with recent-onset psychosis was effective in improving recovery, functioning, psychotic symptoms, insight into illness and treatment, service satisfaction, duration of re-hospitalisations, and time to hospitalisation over an 18-month period. The treatment effects of the PLSMI were significantly greater than those of psychoeducation, particularly at the 12- and 18-month follow-ups.

The PLSMI not only enhanced participants' engagement and empowerment in self-care and help-seeking but also reduced the costs associated with employing psychotherapists. Participant feedback supported the perceived benefits of the PLSMI. Furthermore, guided self-care and recovery planning was more beneficial than the didactic information provided via psychoeducation.

Completion rates were high, while attrition rates were low, for both the PLSMI and PE groups. The PLSMI may be more acceptable than other psychosocial interventions for patients with early psychosis, which typically demonstrate intervention completion rates of 40% to 80% and attrition rates of 15% to 55%.[2,4,5] This PLSMI was user-friendly and required less manpower, making it a feasible option for early intervention.

There were some limitations in the present study. First, participants were volunteers motivated to engage in their illness self-management and recovery; they were not blinded to intervention allocation, which may have introduced expectation and response biases. Second, the sample consisted of patients with relatively high education levels, above-average household income, and a short duration of illness (≤3 years); our findings may not

TABLE 1. Baseline characteristics of participants (n=180)

Characteristic	Peer-led self-management intervention (n=60)	Psychoeducation (n=60)	Treatment as usual (n=60)	P value
Sex				0.15
Male	36 (60.0)	34 (56.7)	36 (60.0)	
Female	24 (40.0)	26 (43.3)	24 (40.0)	
Age, y	25.5±5.8	25.0±6.2	26.1±6.0	0.12
18-25	28 (46.7)	27 (45.0)	26 (43.3)	
26-30	18 (30.0)	17 (28.3)	17 (28.3)	
31-35	10 (16.6)	11 (18.3)	12 (20.0)	
36-43	4 (6.7)	5 (8.3)	5 (8.3)	
Education level				0.18
Primary school or below	9 (15.0)	8 (13.3)	10 (16.7)	
Secondary school	39 (65.0)	38 (63.3)	40 (66.7)	
University or postgraduate degree	12 (20.0)	14 (23.3)	10 (16.7)	
Monthly household income, HK$	19 125±6482	18 553±5275	16 393±5518	0.20
5000-10 000	9 (15.0)	7 (11.7)	10 (16.7)	
10 001-15 000	23 (38.3)	24 (40.0)	23 (38.3)	
15 001-25 000	19 (31.7)	19 (31.7)	18 (30.0)	
25 001-35 000	9 (15.0)	10 (16.7)	9 (15.0)	
Employment status				0.20
Full-time	25 (41.7)	25 (41.7)	27 (45.0)	
Part-time	19 (31.7)	20 (33.3)	19 (31.7)	
Unemployed	16 (26.7)	15 (25.0)	14 (23.3)	
Duration of illness, m	14.82±9.85	15.70±10.10	16.45±9.25	0.23
1- 8	12 (20.0)	15 (25.0)	13 (21.7)	
9-18	21 (35.0)	20 (33.3)	21 (35.0)	
19-24	14 (23.3)	16 (26.7)	17 (28.3)	
>24	13 (21.7)	9 (15.0)	9 (15.0)	
Services received				0.12
Outpatient department	40 (66.7)	38 (63.3)	42 (70.0)	
Day hospital	5 (8.3)	6 (10.0)	9 (15.0)	
Community Psychiatric Nursing Service / Early Assessment Services for Young People	28 (46.7)	29 (48.3)	26 (43.3)	
Counselling and social or recreational service	8 (13.3)	9 (15.0)	7 (11.7)	
Integrated Community Centres for Mental Wellness	60 (100)	60 (100)	59 (98.3)	
Dosage of medication				0.10
High	10 (16.7)	9 (15.0)	10 (16.7)	
Medium	39 (65.0)	40 (66.7)	38 (63.3)	
Low	11 (18.3)	11 (18.3)	12 (20.0)	
Types of psychotropic drugs				0.18
Atypical	32 (53.3)	33 (55.0)	34 (56.7)	
Typical	19 (31.7)	13 (21.7)	13 (21.7)	
Blended	7 (11.7)	8 (13.3)	10 (16.7)	
Anti-depressant/mood stabiliser	3 (5.0)	4 (6.7)	3 (5.0)	
Others (eg, anxiolytics)	5 (8.3)	4 (6.7)	4 (6.7)	
Questionnaire about the Process of Recovery	37.56±9.01	38.01±8.10	38.12±8.50	0.13
Specific Level of Functioning Scale	30.54±6.42	30.92±5.87	30.82±6.44	0.29
Positive and Negative Syndrome Scale				
Total	108.33±17.82	110.22±11.56	110.12±9.89	0.27
Positive symptoms	31.11±7.80	31.75±6.80	31.20±9.00	0.35
Negative symptoms	28.01±6.50	29.80±7.20	29.56±7.90	0.25
General psychopathology	49.23±9.78	48.67±9.40	49.36±9.80	0.20
Social Problem Solving Inventory-Revised: Short version	45.98±8.16	47.33±7.56	46.98±9.94	0.11
Insight and Treatment Attitude Questionnaire	20.10±8.13	21.52±9.12	21.98±9.10	0.11
Re-hospitalisations				
No.	1.32±0.90	1.45±0.91	1.47±0.89	0.12
Duration, d	19.52±6.85	20.05±8.84	18.90±9.12	0.10
No. of patients	29	28	29	0.28

TABLE 2. Outcomes of three intervention groups across five timepoints and results of generalised estimating equation analysis

Outcome	Peer-led self-management intervention (n=58)*	Psychoeducation (n=57)*	Treatment as usual (n=56)*	Generalised estimating equation analysis		
				Group effect†	Time effect†	Group × time effect†
Questionnaire about the Process of Recovery				0.67 (0.36-0.99), P=0.002	0.48 (0.30-0.66), P=0.007	1.98 (1.52-2.44), P=0.001, η^2=0.21
Baseline	37.56±9.01 (28.53-46.62)	38.01±8.10 (29.98-46.31)	38.12±8.50 (29.60-36.80)			
1 week	43.85±9.82 (33.02-52.44)	40.81±8.21 (32.50-49.12)	36.08±9.81 (26.17-46.08)			
6 months	49.98±11.05 (38.61-61.43)	42.50±9.22 (32.28-51.75)	34.42±8.31 (26.11-42.83)			
12 months	52.81±12.65 (40.28-65.40)	43.01±9.60 (34.22-52.58)	36.98±9.77 (27.12-46.75)			
18 months	55.98±11.10 (43.91-66.02)	45.11±10.23 (34.90-55.10)	38.11±10.33 (28.01-48.44)			
Specific Level of Functioning Scale				0.68 (0.38-0.98), P=0.001	0.65 (0.39-0.91), P=0.003	2.01 (1.58-2.44), P=0.001, η^2=0.23
Baseline	30.54±6.42 (23.88-36.93)	30.92±5.87 (24.98-36.74)	30.82±6.44 (24.38-37.24)			
1 week	35.41±6.81 (28.62-42.14)	31.04±6.95 (24.09-37.82)	28.18±7.12 (21.05-35.25)			
6 months	42.82±9.96 (32.86-52.78)	33.83±7.06 (26.78-40.90)	28.94±9.28 (19.83-38.12)			
12 months	43.91±9.12 (34.80-53.02)	37.12±8.43 (28.85-43.51)	30.15±9.45 (20.78-39.60)			
18 months	49.12±9.84 (39.91-49.00)	38.22±8.30 (30.00-46.50)	33.41±9.38 (24.13-42.82)			
Positive and Negative Syndrome Scale				-0.58 (-0.69 to 0.47), P=0.007	-0.52 (-0.73 to -0.31), P=0.01	-1.50 (-2.28 to -0.72), P=0.005, η^2=0.16
Baseline	108.33±17.82 (91.42-126.23)	110.22±11.56 (98.66-121.79)	110.12±9.89 (100.81-120.13)			
1 week	99.30±15.20 (83.83-114.52)	99.96±13.21 (86.70-113.12)	118.21±11.10 (107.14-129.31)			
6 months	85.20±16.04 (69.82-101.22)	98.18±18.51 (80.68-116.63)	122.82±12.81 (110.02-134.03)			
12 months	84.12±14.01 (70.10-98.12)	95.12±11.06 (84.06-106.17)	113.11±9.06 (104.10-122.17)			
18 months	81.01±12.06 (69.04-93.07)	93.22±9.81 (83.46-103.12)	104.98±12.11 (92.99-117.06)			
Social Problem Solving Inventory-Revised: Short version				0.40 (0.25-0.55), P=0.04	0.32 (0.20-0.42), P=0.06	1.11 (0.98-1.24), P=0.06, η^2=0.05
Baseline	45.98±8.16 (37.82-54.13)	47.33±7.56 (39.78-54.88)	46.98±9.94 (37.04-56.93)			
1 week	50.23±9.17 (41.20-59.50)	50.02±8.16 (41.82-58.16)	47.87±9.51 (38.37-57.38)			
6 months	54.12±8.98 (45.13-63.14)	51.82±9.01 42.75-60.80)	48.83±11.03 (37.80-49.87)			
12 months	55.33±5.98 (49.71-61.32)	50.98±8.06 (42.91-59.06)	46.88±8.06 (38.80-54.93)			
18 months	57.11±7.35 (49.80-64.50)	52.11±9.13 (43.00-61.25)	49.33±9.45 (39.98-58.77)			

* Data are presented as mean ± standard deviation (95% confidence interval).

† Data are presented as β (95% confidence interval).

TABLE 2. (cont'd)

Outcome	Peer-led self-management intervention (n=58)*	Psychoeducation (n=57)*	Treatment as usual (n=56)*	Generalised estimating equation analysis		
				Group effect†	Time effect†	Group × time effect†
Insight and Treatment Attitude Questionnaire				0.53 (0.28-0.76), P=0.01	0.46 (0.32-0.60), P=0.02	1.40 (1.05-1.75), P=0.01, η^2=0.13
Baseline	20.10±8.13 (11.98-28.22)	21.52±9.12 (12.40-30.64)	21.98±9.10 (12.88-31.08)			
1 week	24.02±9.80 (15.20-24.02)	20.83±8.04 (12.79-28.88)	18.52±8.02 (10.50-26.54)			
6 months	25.14±9.41 (15.96-34.54)	19.83±8.81 (11.03-28.63)	17.81±9.21 (8.61-27.02)			
12 months	25.48±6.46 (19.02-31.94)	20.31±8.06 (12.30-28.37)	18.12±8.91 (9.21-27.04)			
18 months	26.31±7.30 (19.01-33.40)	21.98±9.36 (12.62-31.31)	17.21±6.06 (11.15-23.28)			
No. of re-hospitalisations				0.38 (0.20-0.56), P=0.06	0.22 (0.13-0.31), P=0.10	0.81 (0.52-1.10), P=0.09, η^2=0.05
Baseline	1.32±0.90 (0.42-2.21)	1.42±0.91 (0.51-2.33)	1.47±0.89 (0.58-2.36)			
1 week	1.02±0.81 (0.21-2.02)	1.33±1.00 (0.33-2.33)	1.40±0.92 (0.48-2.32)			
6 months	1.05±0.72 (0.33-1.77)	1.38±1.02 (0.36-2.40)	1.31±0.98 (0.38-2.29)			
12 months	0.98±0.58 (0.40-1.56)	1.24±0.90 (0.34-2.14)	1.40±0.90 (0.50-2.30)			
18 months	0.98±0.70 (0.28-1.68)	1.09±0.89 (0.21-1.94)	1.33±0.88 (0.75-2.21)			
Duration of re-hospitalisation, d				-0.52 (-0.78 to 0.26), P=0.01	-0.54 (-0.70 to -0.38), P=0.01	-1.50 (-1.89 to -1.11), P=0.01, η^2=0.15
Baseline	19.52±6.85 (12.67-26.37)	20.05±8.84 (11.21-28.89)	18.90±9.12 (9.78-28.02)			
1 week	14.31±7.87 (6.44-22.18)	16.21±9.00 (7.21-25.21)	20.80±9.91 (10.89-30.80)			
6 months	12.84±8.13 (4.71-20.93)	10.89±9.12 (10.77-20.01)	22.50±9.39 (13.11-31.89)			
12 months	9.96±5.23 (4.73-14.19)	12.22±8.01 (4.20-20.23)	18.12±9.06 (9.08-27.16)			
18 months	9.01±4.06 (5.00-13.05)	14.81±7.12 (7.70-21.92)	17.93±8.82 (9.12-27.74)			
No. of patients with re-hospitalisation						P=0.01
Baseline	20	21	19			
1 week	12	17	20			
6 months	7	15	19			
12 months	9	14	15			
18 months	7	12	16			
Client Satisfaction Questionnaire				0.50 (0.24-0.74), P=0.01	0.46 (0.26-0.66), P=0.02	1.32 (1.03-1.61), P=0.02, η^2=0.13
Baseline	15.01±5.02 (9.99-20.03)	15.52±6.80 (8.72-22.32)	15.02±7.20 (7.82-22.22)			
1 week	19.57±7.33 (12.24-27.0)	17.81±8.88 (8.93-26.69)	17.08±9.81 (7.27-26.89)			
6 months	20.98±6.18 (14.80-26.98)	19.02±8.10 (10.98-27.12)	15.33±7.31 (8.02-22.64)			
12 months	21.11±6.01 (15.10-27.14)	19.01±5.89 (13.12-24.90)	18.10±9.10 (9.98-27.18)			
18 months	23.58±7.31 (16.21-30.90)	18.03±6.91 (11.14-24.91)	18.31±9.51 (8.80-27.81)			

be generalisable to the broader patient population. Third, the sample size estimation was based on three similar studies conducted immediately post-intervention; the sample size or study power might be insufficient. Fourth, the PLSMI included only patients; it did not assess family members or relatives who may have interdependent social and healthcare needs related to psychiatric rehabilitation. Finally, problem-solving and self-care practices facilitated by peer support workers in the PLSMI were not systematically monitored.

Conclusion

The PLSMI for individuals with early-stage psychosis is effective in improving psychosocial health outcomes and reducing relapse risk. Our findings support the PLSMI's utility for early intervention in community-based psychosis care, where manpower and resources are limited. Further cost-effective analysis studies are warranted.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#17180291). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Chien WT, Ho LK, Gray R, Bressington D. A randomised controlled trial of a peer-facilitated self-management program for people with recent-onset psychosis. Schizophr Res 2022;250:22-30.

Acknowledgements

The authors thank staff in the six Integrated Community Centres for Mental Wellness for assistance with participant recruitment.

References

1. National Collaborating Centre for Mental Health. Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care. London: British Psychological Society/ Royal College of Psychiatrists; 2016.
2. Stevens J. Applied Multivariate Statistics for the Social Sciences. 4th ed. New Jersey: Erlbaum, Mahwah; 2002.
3. Johnson S, Lamb D, Marston L, et al. Peer-supported self-management for people discharged from a mental health crisis team: a randomized controlled trial. Lancet 2018;392:409-18.
4. Chien WT, Bressington D. A randomized controlled clinical trial of a nurse-led structured psychosocial intervention program for people with first-onset mental illness in psychiatric outpatient clinics. Psychiatry Res 2015;229:277-86.
5. Lally J, Ajnakina O, Stubbs B, et al. Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. Br J Psychiatry 2017;211:350-8.

Return to work and work productivity in patients with breast cancer: a longitudinal study (abridged secondary publication)

WWT Lam *, R Fielding, A Mehnert, A Kwong, M Chan, A Or, D Fong, A Molasiotis, W So, S Chan

KEY MESSAGES

1. Among patients with breast cancer, 52% returned to work within 24 months after surgery, although some required up to 284 days until workforce re-entry.
2. Older age, extensive surgery, chemo- and/or radiotherapy, and unfavourable working condition (prolonged sitting) were barriers to return to work.
3. Higher monthly household income and the presence of financial difficulties were factors associated with return to work.
4. The presence of nausea at baseline predicted greater absenteeism at 24 months post-surgery.
5. Excessive job demands predicted greater loss in a patient's work ability and performance at 24 months post-surgery.

Hong Kong Med J 2024;30(Suppl 7):S28-32
HMRF project number: 15161641

[1] WWT Lam, [1] R Fielding, [2] A Mehnert, [3] A Kwong, [4] M Chan, [4] A Or, [5] D Fong [5,6] A Molasiotis, [7] W So, [8] S Chan

[1] *School of Public Health, The University of Hong Kong, Hong Kong SAR, China*
[2] *University Medical Center, The University of Leipzig, Germany*
[3] *Department of Surgery, The University of Hong Kong, Hong Kong SAR, China*
[4] *Kwong Wah Hospital, Hong Kong SAR, China*
[5] *School of Nursing, The University of Hong Kong, Hong Kong SAR, China*
[6] *School of Nursing, Hong Kong Polytechnic University, Hong Kong SAR, China*
[7] *The Nethersole School of Nursing, The Chinese University of Hong Kong, Hong Kong SAR, China*
[8] *Department of Surgery, United Christian Hospital, Hong Kong SAR, China*

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

Introduction

Breast cancer is the most common cancer among women, both in Hong Kong and worldwide. A substantial number of women diagnosed with breast cancer are of working age, highlighting the need to examine issues regarding return to work (RTW) after cancer diagnosis. RTW indicates reintegration into normal life, which is essential for preserving self-identity and enhancing psychological well-being.[1] Facilitating RTW is economically beneficial, enhances productivity, and therefore has high societal value. However, less attention has been directed towards the impact of cancer diagnosis on work productivity including absenteeism (ie, missing time from work), presenteeism (ie, reduced performance while at work), and activity impairment. Thus, we aimed to examine RTW status and time to RTW, work productivity (absenteeism and presenteeism), and activity impairment among women diagnosed with breast cancer after completion of primary breast cancer treatment, and to identify factors associated with RTW status, time to RTW, work productivity, and activity impairment.

Based on factors proposed by Mehnert,[1] we examined whether time to RTW and work productivity and activity impairment were related to demographic factors (ie, age, education level, and marital status), physical functioning, psychosocial functioning, work satisfaction, and work-related factors. We also investigated whether the effects of medical factors on time to RTW and work productivity were mediated by their effects on physical and psychosocial functioning, work satisfaction, and work-related factors, and whether there were interactions between medical factors and demographic factors in terms of time to RTW and work productivity.

Methods

Consecutive Chinese patients aged ≥18 years who were newly diagnosed with non-metastatic breast cancer, had paid or self-employment at the time of diagnosis, and underwent surgery as primary treatment within 4 weeks of diagnosis were recruited from three public breast care units in Hong Kong between December 2018 and November 2020. Patients with linguistic or intellectual difficulties or a diagnosis of metastatic breast cancer were excluded.

Eligible patients were identified by clinicians at each study unit and then approached by a trained research assistant while awaiting post-surgical follow-up consultations. Patients were asked to complete a baseline questionnaire immediately (T1). Follow-up assessments were conducted via telephone interviews at 4 months (T2), 6 months (T3), 12 months (T4), 18 months (T5), and 24 months (T6).

Medical data were retrieved from hospital medical records using a standardised medical information profile.

RTW was defined as the time needed to return to work after an absence due to the cancer diagnosis (ie, time off from work, including paid or unpaid sick leave).[1] At each assessment (T1-T6), patients were asked to indicate whether they were continuing sick leave; if they had RTW, they were asked to specify the date of RTW. Time to RTW was defined as the number of days between the first day of sick leave due to the breast cancer and the first day of RTW, irrespective of any changes in job nature (eg, new job, different job responsibilities, or reduced working hours).[1]

Work productivity and activity impairment were assessed using the Chinese version of the Work Productivity and Activity Impairment questionnaire, with a recall period of 7 days.[2] The six-item questionnaire measures four domains: absenteeism (number of work hours missed due to current health condition), presenteeism (extent to which the current health condition affects productivity at work), work productivity loss (extent of work inability induced by the current health condition), and activity impairment (extent to which the current health condition affected regular activities other than work).

Work satisfaction was measured using the 12-item Work Satisfaction Scale[3] on a seven-point Likert scale. Patients rated their satisfaction with various aspects of work such as co-workers, working condition, and working hours.

Perceived job strain (eg, working overtime, time pressure, and high pressure of competition) was assessed using a 10-item scale,[3] and working condition (eg, physically heavy work and under-challenging work) were assessed using an eight-item scale.[3]

Physical and psychosocial functioning were assessed using the standard Chinese versions of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and the breast cancer-specific module.[4] The former comprises 30 items across five functional domains (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, pain, and nausea/vomiting), a global health-related quality of life subscale, five single-symptom items (dyspnoea, appetite loss, sleep disturbance, constipation, and diarrhoea), and financial difficulties. The latter is a breast cancer-specific measure consisting of 23 items across four functional domains (body image, sexual functioning, sexual enjoyment, and future perspective) and four symptom scales (arm symptoms, breast symptoms, adverse effects of systemic therapy, and being upset by hair loss).[4]

Kaplan-Meier survival analysis was used to estimate the mean time to RTW. Cox regression analysis was performed to identify factors associated with RTW status. Hazard ratios (HRs) represent the RTW probability; an HR of >1 indicates an increased likelihood of work resumption. Linear regression analyses were performed to identify covariates of time to RTW, work productivity, and activity impairment. The coefficient B or beta indicates the direction of each association between outcome variables and covariates. Bonferroni correction was used to calculate adjusted P-values for multiple comparisons.

Results

Of 532 eligible patients, 378 (71%) agreed to participate and completed baseline assessment. Of these, 311 were included in the analysis who completed assessment at 4 months (n=289), 6 months (n=263), 12 months (n=225), 18 months (n=161), and/or 24 months (n=145) [Table 1]. Attrition rates for follow-up assessments ranged from 23.5% to 61.6%. The remaining 67 patients were excluded from analysis due to death, diagnosis with stage 4 disease, or absence of ≥3 follow-up assessments.

The rate of RTW ranged from 22.8% to 70.6% across the six timepoints (Table 2). On average, 52.36% of the patients returned to work within 24 months after surgery. Kaplan-Meier survival analysis showed that the average time to RTW was 9.47 months (standard error=0.50). It is estimated that 75% and 25% of the patients remained out of the workforce at 2.77 months and 15.33 months, respectively.

In the multivariable Cox regression model, higher monthly household income (>HK$30 000 per month) [HR=2.22, P<0.001] and more prolonged sitting at work (HR=1.28, P<0.001) were associated with a higher likelihood of work resumption within 24 months after surgery. Conversely, extensive surgery (mastectomy with/without reconstruction) [HR=0.60, P<0.001], chemotherapy (HR=0.51, P<0.001), radiotherapy (HR=0.55, P<0.001), and greater financial difficulties (HR=0.99, P=0.045) were associated with a lower likelihood of work resumption (Table 2).

In the multivariable linear regression model, older age (B=0.16, P=0.050), extensive surgery (mastectomy with/without reconstruction) [B=2.57, P=0.020], chemotherapy (B=4.07, P<0.001), and radiotherapy (B=3.27, P=0.010) were associated with a longer time to RTW. In contrast, perceived working condition that involved more prolonged sitting (B=-1.48, P=0.020) was associated with a shorter time to RTW (Table 3).

Extensive surgery (mastectomy with/without reconstruction) was positively associated with a longer time to RTW (β=3.98, P=0.001) but negatively

TABLE 1. Clinical characteristics of patients (n=311)

Characteristic	Value*
Age at diagnosis, y	52.62±8.18
Time since cancer diagnosis, m	4.34±7.62
Marital status	
Married/cohabited	186 (59.8)
Single/divorced/separated/widowed	124 (39.9)
Missing	1 (0.3)
Education level	
No formal/primary education	43 (13.8)
Secondary/tertiary	266 (85.5)
Missing	2 (0.6)
Job title	
White collar	116 (37.3)
Blue collar	132 (42.4)
Professional, manager, or self-employed	63 (20.3)
Monthly household income, HK$	
<10 000	56 (18.0)
10 001-30 000	124 (39.9)
≥30 001	122 (39.2)
Missing data	9 (2.9)
Surgery type	
Breast conserving (including axillary lymph node dissection)	150 (48.2)
Mastectomy or plus reconstruction	160 (51.4)
Missing data	1 (0.3)
Active treatment at baseline	
Chemotherapy	64 (20.6)
Radiotherapy	24 (7.7)
Target therapy	36 (11.6)
Hormonal therapy	58 (18.6)
No active treatment	191 (61.4)
Missing data	0
Active treatment at 4 months	
Chemotherapy	65 (20.9)
Radiotherapy	32 (10.3)
Target therapy	41 (13.2)
Hormonal therapy	130 (41.8)
No active treatment	57 (18.3)
Missing data	48 (15.4)
Active treatment at 6 months	
Chemotherapy	25 (8.0)
Radiotherapy	30 (9.6)
Target therapy	37 (11.9)
Hormonal therapy	151 (48.6)
No active treatment	77 (24.8)
Missing data	45 (14.5)
Active treatment at 12 months	
Chemotherapy	3 (1.0)
Radiotherapy	6 (1.9)
Target therapy	20 (6.4)
Hormonal therapy	143 (46.0)
No active treatment	73 (23.5)
Missing data	77 (24.8)
Active treatment at 18 months	
Chemotherapy	3 (1.0)
Radiotherapy	0
Target therapy	5 (1.6)
Hormonal therapy	120 (38.6)
No active treatment	43 (13.8)
Missing data	146 (46.9)
Active treatment at 24 months	
Chemotherapy	3 (1.0)
Radiotherapy	2 (0.6)
Target therapy	3 (1.0)
Hormonal therapy	98 (31.5)
No active treatment	42 (13.5)
Missing data	165 (53.1)

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

associated with physical (β= -8.61, P<0.001) and role (β= -6.70, P=0.033) functioning. Physical (β= -0.10, P<0.001) and role (β= -0.051, P=0.0046) functioning were both negatively associated with a shorter time to RTW, indicating putative mediation effects. Bootstrapping procedures with 5000 iterations were performed to test mediation effects.[5] Extensive surgery had indirect effects on time to RTW mediated through physical (β=0.86, 95% confidence interval [CI]=0.28-1.63) and role (β=0.34, 95% CI=0.014-0.87) functioning. After controlling for these two mediators, the direct effect of extensive surgery on time to RTW remained significant (β=3.12, P=0.015 and β=3.64, P<0.001, respectively). These findings indicate that physical and role functioning independently and partially mediate the association between time to RTW and surgery type.

Chemotherapy was positively associated with a longer time to RTW (β=5.64-5.73, P<0.001) but negatively associated with physical functioning (β= -7.30, P=0.015) and work satisfaction (β= -0.28, P=0.026). Physical functioning (β= -0.095, P=0.001) and work satisfaction (β= -1.91, P<0.001) were negatively associated with a shorter time to RTW, indicating putative mediation effects. Using the

TABLE 2. Predictors of work resumption in multivariable Cox regression model (n=302) [χ^2=108.88, P<0.001]

Variable	B	Standard error	Hazard ratio (95% confidence interval)	P value	Adjusted P value
Monthly household income, HK$					
10 000 (reference)					
10 001-30 000	0.40	0.22	1.48 (0.96-2.29)	0.074	0.67
≥30 001	0.80	0.22	2.22 (1.48-3.44)	<0.001	<0.001
Surgery type					
Breast conserving (including axillary lymph node dissection) [reference]					
Mastectomy or plus reconstruction	-0.51	0.14	0.60 (0.46-0.80)	<0.001	<0.001
Chemotherapy	-0.67	0.15	0.51 (0.38-0.69)	<0.001	<0.001
Radiotherapy	-0.60	0.17	0.55 (0.39-0.77)	<0.001	<0.001
Working condition					
Incorrect one-sided posture	-0.17	0.081	0.84 (0.72-0.99)	0.033	0.30
Frequent/long hours in sitting position	0.24	0.073	1.28 (1.11-1.47)	<0.001	<0.001
Financial difficulties	-0.007	0.002	0.99 (0.98-0.99)	0.005	0.045

TABLE 3. Predictors of time to return to work in multivariable linear regression model (n=311) [R^2=0.33, P<0.001]

Variable	B (95% confidence interval)	β	t	P value	Adjusted P value
Age	0.16 (0.047 to 0.26)	0.15	2.82	0.005	0.05
Monthly household income, HK$					
10 000 (reference)					
10 001-30 000	-	-	-	-	-
≥30 001	-2.52 (-4.40 to -0.65)	-0.15	-2.65	0.008	0.080
Surgery type					
Breast conserving (including axillary lymph node dissection) [reference]					
Mastectomy or plus reconstruction	2.57 (0.81-4.33)	0.15	2.87	0.004	0.040
Chemotherapy	4.07 (2.26-5.87)	0.23	4.43	<0.001	<0.001
Radiotherapy	3.27 (1.28-5.25)	0.17	3.25	0.001	0.010
Frequent/long hours in sitting position	-1.48 (-2.40 to -0.57)	-0.16	-3.19	0.002	0.020
Physical functioning	-0.042 (-0.091 to 0.007)	-0.096	-1.68	0.095	0.95
Financial difficulties	0.38 (0.007 to 0.068)	0.14	2.44	0.015	0.15

same bootstrapping procedures,[5] Chemotherapy had indirect effects on time to RTW mediated through physical functioning (β=0.70, 95% CI=0.20-1.39) and work satisfaction (β=0.53, 95% CI=0.05-1.14). After controlling for these two mediators, the direct effect of chemotherapy on time to RTW remained significant (β=4.94, P<0.001 and β=5.20, P<0.001, respectively). These results indicate that physical functioning and work satisfaction independently and partially mediate the association between time to RTW and chemotherapy.

Radiotherapy was positively associated with a longer time to RTW (β=4.44, P<0.001) but negatively associated with work satisfaction (β= -0.33, P=0.016). Work satisfaction (β= -2.00, P<0.001) was negatively associated with a shorter time to RTW, indicating putative mediation effects. Radiotherapy had indirect effects on time to RTW mediated through work satisfaction (β=0.67, 95% CI=0.10-1.35). After controlling for this mediator, the direct effect of radiotherapy on time to RTW remained significant (β=3.77, P<0.001), which indicates that work satisfaction partially mediates the association between time to RTW and radiotherapy.

Moderation analysis showed significant interactions of chemotherapy × age (β=0.27,

P=0.026) and chemotherapy × education level (β= -6.61, P=0.015) with time to RTW, suggesting that age and education level independently moderate the association between time to RTW and chemotherapy.

In analyses of factors associated with work productivity and activity impairment at 24 months post-surgery, only patients with active employment at 24 months were able to report their working hours and absence from work. Therefore, absenteeism and presenteeism data were not applicable to patients who were on sick leave or unemployed. At 24 months, 11.5% of active employment reported absenteeism due to their health condition. On average, their absence constituted 3.76% of their working time. In multivariable regression model, nausea (B=0.31, 95% CI=0.078-0.55, P=0.020) was positively associated with absenteeism. Additionally, 54% of the patients with active employment reported work impairment due to their health condition (ie, presenteeism). In the multivariable regression model, only perceived working condition with excessive demands remained a significant factor. Greater perceived work demands were associated with higher levels of presenteeism (B=8.18, 95% CI=0.41-15.94, P=0.040). Moreover, 25.10% of patients reported activity impairment due to their health condition. In multivariable regression model, only role functioning was negatively associated with activity impairment (B= -0.14, 95% CI= -0.26 to -0.22, P=0.021). Only physical functioning was a mediator of the association between activity impairment and hormonal therapy. Hormonal therapy was positively associated with activity impairment (β=14.21, P=0.0045) but negatively associated with physical functioning (β= -8.02, P=0.035). Physical functioning was negatively associated with activity impairment (β= -0.34, P=0.010), indicating putative mediation effects. Hormonal therapy had an indirect effect on activity impairment mediated through physical functioning (β=2.76, 95% CI=0.31-6.28). After controlling for the mediator, the direct effect of hormonal therapy on activity impairment remained significant (β=11.45, P=0.019), indicating that physical functioning partially mediates the association between activity impairment and hormonal therapy.

Discussion

Cancer diagnosis and treatment can affect RTW, work productivity, and activity impairment. RTW after cancer treatment can be challenging, especially during the initial recovery stage, as evidenced by the low rate of RTW at baseline. The time to RTW varies among patients; some individuals require up to 284 days to re-enter the workforce.

Our findings partially support Mehnert's explanation of work-related outcomes in cancer survivorship.[1] Older age, lower monthly household income, extensive surgery, chemo- and/or radiotherapy, unfavourable working condition (prolonged sitting), and financial difficulties were barriers to RTW. Specifically, physical functioning partially mediated the associations between RTW and both surgery type and chemotherapy; role functioning partially mediated the association between RTW and surgery type; and work satisfaction mediated the associations between RTW and both chemo- and radiotherapy. The impact of chemotherapy on RTW was strengthened by older age but weakened by higher education levels.

The physical symptom of nausea can result in absenteeism. A stressful work environment with excessive demands can adversely affect a patient's work ability and performance. Poor role functioning, and the indirect effect of hormonal therapy mediated through physical functioning, can impair a patient's ability to perform regular activities.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#15161641). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Ng DWL, So SCY, Fielding R, et al. Return to work, work productivity loss and activity impairment in Chinese breast cancer survivors 12-month post-surgery: a longitudinal study. Front Public Health 2024;12:1340920.

References

1. Mehnert A. Employment and work-related issues in cancer survivors. Crit Rev Oncol Hematol 2011;77:109-30.
2. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353-65.
3. Bürger W, Dietsche S, Morfeld M, Koch U. Multiperspective estimates on the probability of patient return to work following orthopaedic rehabilitation: findings and predictive relevance [in German]. Rehabilitation (Stuttg) 2001;40:217-25.
4. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365-76.
5. Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis: a Regression-Based Approach. New York: Guilford Press; 2018.

Neurocognitive impairment after intensity-modulated radiotherapy in patients with nasopharyngeal cancer: association with radiation dose and retinal vascular characteristics (abridged secondary publication)

JCH Chow *, BCY Zee, AYL Lau, KH Au, AMC Lau

KEY MESSAGES

1. Neurocognitive impairment is prevalent among nasopharyngeal carcinoma survivors who underwent definitive intensity-modulated radiotherapy.
2. Significant impairments were observed in multiple neurocognitive domains including verbal memory, executive function, processing speed, motor dexterity, and language ability.
3. Radiation doses to the whole brain, hippocampus, and temporal lobe were associated with neurocognitive impairment.
4. Retinal image analysis may be useful to detect neurocognitive impairment.

Hong Kong Med J 2024;30(Suppl 7):S33-6
HMRF project number: 07180166

[1] **JCH Chow,** [2] **BCY Zee,** [3] **AYL Lau,** [1] **KH Au,** [4] **AMC Lau**

[1] *Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong SAR, China*
[2] *Division of Biostatistics, Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong SAR, China*
[3] *Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China*
[4] *Department of Clinical Psychology, Queen Elizabeth Hospital, Hong Kong SAR, China*

* Principal applicant and corresponding author: cch932@ha.org.hk

Introduction

Treatment outcomes for nasopharyngeal carcinoma (NPC) have significantly improved in recent decades.[1] Although intensity-modulated radiotherapy (IMRT) for NPC has greatly enhanced tumour target conformity, a large volume of brain tissue is inevitably exposed to radiation. Previous studies investigating neurocognitive impairment in IMRT-treated patients with NPC were limited by small sample sizes, the use of simple cognitive screening tools, and short follow-up intervals.[2] The pattern and severity of this late complication remain unclear, as does the clinical-dosimetric relationship.

Radiation microangiopathy and the disruption of neurovascular relationships are two major mechanisms of radiation-associated cognitive dysfunction. Retinal characteristics are associated with white matter hyperintensity on magnetic resonance imaging, which is a hallmark of radiation brain injury.[3] Advances in automated machine learning–based analytic algorithms have greatly improved the efficiency and reproducibility of retinal image analysis for detecting various neurological diseases.

This cross-sectional study aimed to determine the prevalence and pattern of neurocognitive impairment in post-IMRT NPC survivors using a comprehensive battery of multidomain neurocognitive assessments. Additionally, associations between radiation dose-volume parameters in brain substructures and retinal characteristics were also investigated.

Methods

Patients with NPC who remained in disease remission for at least 1 year after definitive IMRT were included. All radiotherapy plans were developed using a simultaneous integrated boost technique whereby high-risk clinical target volumes received 66 to 70 Gy and low-risk volumes received 54 to 60 Gy, both delivered in 33 fractions.

Participants were evaluated using the Montreal Cognitive Assessment-Hong Kong and the Depression Anxiety Stress Scale. Subsequently, neurocognitive functions across eight domains were assessed using the Wechsler Adult Intelligence Scale-IV for intellectual capacity, Wechsler Adult Intelligence Scale-IV Digit Span for attention span, Wechsler Memory Scale-III for visual-spatial span, Wechsler Memory Scale-III Visual Reproduction Span for visual memory, Auditory Verbal Learning Test for verbal memory, Trail Making Test for processing speed, Stroop Test for executive function, Grooved Pegboard Test for motor dexterity, and Verbal Fluency Test for language ability. Raw scores were normalised to participant age and educational level, expressed as percentiles or Z-scores. Neurocognitive performance was categorised as follows: normal (≥25th percentile or Z-score ≥ -0.67), low average (9th-24th percentile or Z-score -1.33 to

-0.68), borderline impairment (3rd-8th percentile or Z-score -2.00 to -1.34), impairment (1st-2nd percentile or Z-score -2.50 to -2.01), and profound impairment (<1st percentile or Z-score < -2.50).

The IMRT plans for all participants were retrieved. The whole brain and various substructures (eg, frontal lobe, parietal lobe, temporal lobe, occipital lobe, hippocampus, pituitary gland, hypothalamus, thalamus, and cerebellum) were delineated on simulation computed tomography images in accordance with standardised atlases. Radiation dose-volume parameters were collected for each brain sub-structure; these included maximum dose, minimum dose, mean dose, median dose, and volume-based metrics.

Retinal images of both eyes were captured. Vascular features such as retinal vessel measurements, arteriole-venous nicking, arteriole occlusion, haemorrhages, exudates, tortuosity, bifurcation coefficients, branch asymmetries, and bifurcation angles were evaluated using a machine learning–based algorithm. This automated approach incorporated fractal analysis, high-order spectra analysis, and statistical texture analyses.

Mean age-normalised and education level–normalised percentiles and Z-scores from the neurocognitive assessments were compared with the 50th percentile and a Z-score of 0 using one-sample *t*-tests. Associations between neurocognitive outcomes and radiation doses to brain substructures were determined using multivariable logistic regression. Model generation was restricted to neurocognitive domains with a sufficient number of impaired cases for robust analysis.

Results

In total, 190 NPC survivors were enrolled between 15 December 2020 and 8 July 2022 (Table 1). The median interval from IMRT completion to neurocognitive assessment was 7.0 (range, 1.0-13.6) years. The mean Montreal Cognitive Assessment score was 23.6; 48 (25.3%) participants were classified as cognitively impaired according to age- and education-level-adjusted cut-offs. Additionally, 4.7%, 18.5%, and 4.2% of participants exhibited severe or very severe depression, anxiety, or stress, respectively.

In total, 182 participants completed all domain-specific neurocognitive assessments. Of these participants, 79.4% demonstrated impairment in at least one neurocognitive domain. Compared with normative population references, participants showed significant impairments across multiple neurocognitive domains (Fig). Regarding visual memory, participants performed worse in delayed recall (mean percentile difference= -4.15, P=0.027), image copying (mean percentile difference= -4.47, P=0.009), and retention of graphical memory (mean percentile difference= -9.27, P<0.001). Significant impairments were also observed in short-term (mean Z-score= -0.56, P<0.001) and long-term (mean Z-score= -0.70, P<0.001) retention of verbal memory. Regarding executive function, significant impairments were detected in the ability to inhibit cognitive interference (mean Z-score= -1.90, P<0.001). Regarding processing speed, reaction times to complete the basic (mean Z-score= -1.04, P<0.001) and advanced (mean Z-score= -0.38, P<0.001) coloured trails were prolonged. Regarding motor dexterity, participants required longer time to complete the grooved pegboard test with both the dominant (mean Z-score= -0.97, P<0.001) and non-dominant (mean Z-score= -0.93, P<0.001) hands. Participants also demonstrated impaired language ability (mean Z-score= -0.29, P=0.001). No significant impairments in intellectual quotient or attention span were observed.

Radiation doses to brain substructures were extracted from the IMRT plans of 145 participants. The average mean dose to the whole brain was 11.87 Gy. Among the four cerebral lobes, the temporal lobe received the highest average mean dose of 19.82 Gy, followed by the occipital, parietal, and frontal lobes, which had average mean doses of 14.42 Gy, 4.68 Gy, and 2.74 Gy, respectively. The average mean and maximum doses to the hippocampus were 25.82 Gy and 50.03 Gy, respectively.

Domain-specific neurocognitive impairments were associated with radiation dose-volume parameters in multiple brain substructures. The radiation dose to the whole brain was positively associated with impairments in executive function (odds ratio [OR]=1.120, 95% confidence interval [CI]=1.032-1.215, P=0.007) and motor dexterity of the dominant hand (OR=1.003, 95% CI=1.001-1.006, P=0.018). The maximum dose to the hippocampus was associated with worse short-term (OR=1.001, 95% CI=1.000-1.002, P=0.019) and long-term (OR=1.001, 95% CI=1.000-1.001, P=0.080) retention of verbal memory. The maximum dose to the temporal lobe was associated with impaired processing speed (OR=1.003, 95% CI=1.000-1.006, P=0.047).

In logistic regression models built using clinical and radiation dosimetric data, the area under the curve was 0.664 to 0.864. In models built using retinal characteristics, the area under the curve significantly improved to 0.949 to 0.997 (Table 2); sensitivities were >80% across neurocognitive domains and negative emotions (except for motor dexterity based on dominant-hand reaction time), and corresponding specificities were >90%.

Discussion

We found that >80% of NPC survivors exhibited impairment in at least one neurocognitive domain. The impairments predominantly affected verbal memory, executive function, processing speed, motor dexterity, and language ability, but general

TABLE 1. Characteristics of participants (n=190)

Characteristic	Value*
Age, y	55.5±9.5
Sex	
Male	140 (73.7)
Female	50 (26.3)
Employment status	
Unemployed	31 (16.3)
Employed	112 (59.0)
Retired	47 (24.7)
Education level	
Primary or below	24 (12.6)
Secondary	146 (76.9)
Tertiary or above	20 (10.5)
Smoking	
No	162 (85.3)
Yes	28 (14.7)
Alcohol consumption	
No	159 (83.7)
Yes	30 (15.8)
Unknown	1 (0.5)
Medical comorbidity	
Diabetes mellitus	13 (6.8)
Hypertension	52 (27.4)
Hyperlipidaemia	14 (7.4)
Stroke	2 (1.1)
Others	18 (9.5)
Histology	
Undifferentiated carcinoma	178 (93.7)
Non-keratinising squamous cell carcinoma	8 (4.2)
Keratinising squamous cell carcinoma	4 (2.1)
T-stage	
T1	32 (16.8)
T2	19 (10.0)
T3	116 (61.1)
T4	23 (12.1)
N-stage	
N0	6 (3.2)
N1	38 (20.0)
N2	129 (67.9)
N3	17 (8.9)
American Joint Committee on Cancer stage (8th Edition)	
I	4 (2.1)
II	17 (8.9)
III	130 (68.5)
IVA	39 (20.5)
Chemotherapy	
None	24 (12.6)
Concurrent	108 (56.9)
Concurrent + adjuvant	32 (16.8)
Induction + concurrent	24 (12.6)
Other chemotherapy combinations	2 (1.1)
Montreal Cognitive Assessment-Hong Kong score	23.6±3.7
Impairment using cut-off of <23	62 (32.6)
Impairment using age-/education level–adjusted cut-offs	48 (25.3)
Depression Anxiety Stress Scale	
Depression	
Normal	138 (72.7)
Mild	23 (12.1)
Moderate	20 (10.5)
Severe	5 (2.6)
Extremely severe	4 (2.1)
Anxiety	
Normal	80 (42.1)
Mild	19 (10.0)
Moderate	56 (29.5)
Severe	21 (11.1)
Extremely severe	14 (7.3)
Stress	
Normal	157 (82.6)
Mild	14 (7.4)
Moderate	11 (5.8)
Severe	5 (2.6)
Extremely severe	3 (1.6)

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

intelligence and attention span were relatively unaffected. Considering the relatively young bimodal age distribution of NPC incidence, which peaks at approximately 30 and 55 years, this high prevalence of post-radiation cognitive dysfunction has substantial implications for quality of life, daily activities, social interactions, and work rehabilitation among long-term survivors.

We observed greater deficits in long-term memory retention than in short-term recall for verbal memory. This may be related to the uneven distribution of radiation doses within the brain. The temporal lobe, responsible for memory consolidation and retention, received a high average mean dose of 19.82 Gy because of its proximity to the primary NPC site. In contrast, short-term working memory is primarily governed by the prefrontal cortex in the frontal lobe, which received a relatively low scattered radiation dose of 2.74 Gy. Consistent with this hypothesis, our exploratory dosimetric analyses revealed positive associations

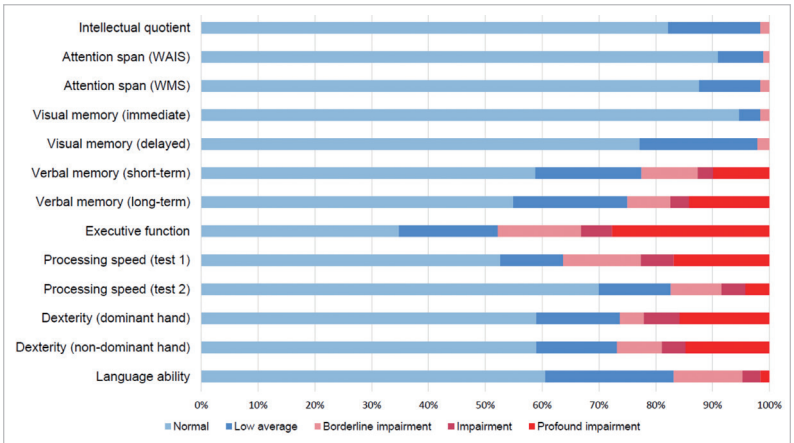


FIG. Patterns and severities of neurocognitive impairment across different domains
Abbreviations: WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale

TABLE 2. Area under the receiver operating characteristic curve in two prediction models

Neurocognitive assessments	No. of participants	Area under the curve	
		Model built using clinical and radiation dosimetric parameters	Model built using retinal image analysis features
Montreal Cognitive Assessment-Hong Kong for global cognitive screening	138	0.694	0.997
Verbal memory			
Short-term retention	131	0.864	0.986
Long-term retention	133	0.654	0.977
Word recognition	132	0.715	0.995
Stroop Test for executive function	136	0.708	0.954
Processing speed			
Colour Trail Test (basic)	138	0.664	0.965
Colour Trail Test (advanced)	138	0.849	0.993
Motor dexterity			
Dominant-hand reaction time	138	0.759	0.949
Non-dominant-hand reaction time	138	0.697	0.985

between the maximum doses to the temporal lobe and hippocampus, suggesting that lower radiation doses to these structures could reduce long-term memory impairments. Careful consideration of the hippocampus during radiotherapy planning may be beneficial. Small pilot studies have demonstrated the dosimetric feasibility of hippocampal-sparing IMRT for NPC without compromising tumour target coverage.[4] Nonetheless, prospective studies are needed to quantify the cognitive benefits of this approach.

Our study highlights the clinical value of incorporating automated retinal image analysis into survivorship care for patients with NPC. Retinal vascular characteristics may serve as indicators for susceptibility to neurological injury from radiation exposure. The machine learning–based image analysis system can detect retinal features specific to radiation damage, which can serve as markers of potential radiation-induced injury to the central nervous system. Currently, there are no established guidelines regarding appropriate screening methods for radiation-associated cognitive decline in NPC survivors. Automated retinal image analysis offers a rapid, efficient, objective, and non-invasive tool to identify high-risk patients for neurocognitive assessment. This approach may be particularly valuable in underserved areas with limited access to neuropsychological specialists.

Conclusions

Neurocognitive impairment is prevalent among NPC survivors after definitive IMRT, affecting multiple cognitive domains including verbal memory, executive function, processing speed, motor dexterity, and language ability. Automated retinal image analysis may be useful to detect post-radiation neurocognitive impairment.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#07180166). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Chow JCH, Lee J, Lai MMP, et al. Multi-domain neurocognitive impairment following definitive intensity-modulated radiotherapy for nasopharyngeal cancer: a cross-sectional study. Radiother Oncol 2024;193:110143.
2. Chow JCH, Ho JCS, Cheung KM, et al. Neurological complications of modern radiotherapy for head and neck cancer. Radiother Oncol 2024;194:110200.

References

1. Au KH, Ngan RKC, Ng AWY, et al. Treatment outcomes of nasopharyngeal carcinoma in modern era after intensity modulated radiotherapy (IMRT) in Hong Kong: a report of 3328 patients (HKNPCSG 1301 study). Oral Oncol 2018;77:16-21.
2. McDowell LJ, Ringash J, Xu W, et al. A cross sectional study in cognitive and neurobehavioral impairment in long-term nasopharyngeal cancer survivors treated with intensity-modulated radiotherapy. Radiother Oncol 2019;131:179-85.
3. Lau AY, Mok V, Lee J, et al. Retinal image analytics detects white matter hyperintensities in healthy adults. Ann Clin Transl Neurol 2019;6:98-105.
4. Gu W, Li Q, Xi D, Tian Y, Mo J, Pei H. The hippocampus sparing volume modulated arc therapy does not influence plan quality on locally advanced nasopharyngeal carcinoma patients. Sci Rep 2017;7:3443.

Regression of liver fibrosis after seroclearance of hepatitis B surface antigen: a prospective matched case-control study using transient elastography and serum Enhanced Liver Fibrosis test (abridged secondary publication)

LY Mak *, MF Yuen, WK Seto, J Fung, DKH Wong

KEY MESSAGES

1. Chronic hepatitis B infection is usually lifelong. Only 0.5% to 2.0% of patients per year achieve functional cure, defined as seroclearance of hepatitis B surface antigen (HBsAg), which is associated with a lower risk of liver cancer.
2. It remains unclear whether HBsAg loss is associated with regression in liver fibrosis.
3. Assessments via imaging (transient elastography) and a serum-based biomarker (Enhanced Liver Fibrosis test score) showed that HBsAg loss was not associated with a higher rate of liver fibrosis regression at 3 years.
4. Age at HBsAg loss has prognostic implications for advanced fibrosis and cirrhosis risks. Patients achieving HBsAg seroclearance after age 50 years should receive ongoing surveillance for liver-related complications.

Hong Kong Med J 2024;30(Suppl 7):S37-9
HMRF project number: 16171251

LY Mak, MF Yuen, WK Seto, J Fung, DKH Wong

Department of Medicine, School of Clinical Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

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

Introduction

Patients with chronic hepatitis B infection (CHB) are at risk for cirrhosis and liver cancer. Only 0.5% to 2.0% of patients per year achieve functional cure, defined as seroclearance of hepatitis B surface antigen (HBsAg). This seroclearance, also known as HBsAg loss, is associated with a lower risk of hepatocellular carcinoma (HCC), especially when it occurs before age 50 years.[1] Risks of liver decompensation, transplantation, and death are also reduced. Nonetheless, it remains uncertain whether HBsAg loss produces similar beneficial effects on cirrhosis.

The use of non-invasive methods, such as the Enhanced Liver Fibrosis (ELF) test and transient elastography, to quantify liver fibrosis is standard care for patients with CHB. The ELF test measures three serum markers of advanced liver fibrosis and cirrhosis, including tissue inhibitor of metalloproteinase 1, amino-terminal pro-peptide of type III pro-collagen, and hyaluronic acid. It has been validated by histology-based studies in patients with CHB. Transient elastography exhibits good performance characteristics for assessing liver fibrosis. It is safe, fast, and reproducible; therefore, it has been widely adopted as a surrogate marker for liver fibrosis.[2] A combination of tests for fibrosis assessment is recommended. The use of both a serum-based test and an imaging-based test (rather than either test alone) may improve diagnostic accuracy and reduce the need for liver biopsies.[3]

We aimed to compare the percentages of patients with fibrosis regression between CHB patients with and without HBsAg loss. We hypothesised that HBsAg loss is associated with ongoing favourable effects on liver fibrosis and increased odds of fibrosis regression.

Methods

Patients with CHB (ie, HBsAg positivity for >6 months) aged 18 to 75 years with spontaneous HBsAg loss (defined as sustained HBsAg negativity for >6 months) were prospectively recruited from the Liver Clinic, Department of Medicine, Queen Mary Hospital, Hong Kong. Matched controls were CHB patients without HBsAg loss who were not receiving antiviral treatment; these controls were recruited at a 1:1 ratio after matching for age and sex. We specifically excluded antiviral-treated patients because such treatment is known to influence fibrosis regression. Patients were also excluded if they had abnormal alanine aminotransferase (ALT) on two occasions separated by >6 months (because elevated ALT confounds liver stiffness [LS] measurement), concomitant liver disease, a prior history of HCC or liver transplantation, or other serious medical conditions. All recruited patients underwent liver assessment by transient elastography and serum

ELF measurement at baseline and 3 years. The age at HBsAg loss and the time since HBsAg loss were recorded.

The controlled attenuation parameter (CAP) for liver steatosis estimation was recorded in decibels per meter (dB/m). Liver fibrosis stages were classified in accordance with European Association for Study of Liver guidelines, as follows: minimal fibrosis (F1) with LS of <6 kPa, grey zone (F2) [6-9 kPa], advanced fibrosis (F3) [9-12 kPa], and cirrhosis (F4) [>12 kPa]. Steatosis was categorised as mild (CAP: 248-267 dB/m), moderate (CAP: 268-279 dB/m), and severe (CAP: ≥280 dB/m). ELF scores of ≥8.5, ≥9.4, and ≥10.1 were defined as F2, F3, and F4, respectively.

The primary outcome was the percentage of patients with fibrosis regression at 3 years between those with and without HBsAg loss. The time interval was chosen based on observations that clinically significant fibrosis regression occurred after disease quiescence was achieved by nucleoside analogue therapy or HBsAg loss for a minimum of 3 years.[4] Fibrosis regression was arbitrarily defined as an LS reduction of ≥30% from baseline. No data were available regarding longitudinal changes in ELF score or a standardised definition of 'significant change'.[5] Therefore, a significant change in ELF score was arbitrarily defined as downstaging (ie, >10.1 to <9.4, >9.4 to <8.5, or >8.5 to <8.5). Analysis was performed according to the intention-to-treat principle; all patients who completed the 3-year follow-up were included in the endpoint analysis.

TABLE. Baseline characteristics of patients with and without hepatitis B surface antigen (HBsAg) loss

Variable	HBsAg loss (n=142)*	No HBsAg loss (n=142)*	P value
Age, y	60 (53.3-66.9)	55.7 (49.5-61.4)	<0.001
Male sex	51.4	51.4	1.000
Overweight	56.3	66.9	0.087
Body mass index, kg/m^2	23.8	24.3	0.185
Controlled attenuation parameter (CAP), dB/m	234 (207-294)	251 (208-297)	0.208
Type 2 diabetes	17.6	18.3	1.000
Alanine aminotransferase, U/L	21 (16-29)	24 (19-31)	0.012
Aspartate aminotransferase, U/L	24 (21-28)	24 (21-31)	0.364
Platelets, ×10^9/L	214 (183-254)	216 (183-250)	0.837
Hepatitis B virus DNA, IU/mL	-	267 (69-887)	-
Age at HBsAg loss, y	57.4 (50.5-63.2)	-	-
Time since HBsAg loss, y	5.5 (4.9-6.2)	-	-
Steatosis (CAP ≥248 dB/m)	43.7	52.1	0.191
Liver stiffness, kPa	5.1 (4.1-6.2)	5.2 (4.3-6.8)	0.420
Advanced fibrosis/cirrhosis (F3/F4)	4.9	3.5	0.770
Enhanced Liver Fibrosis test score	9.3 (8.8-9.9)	8.4 (7.9-9.3)	<0.001
Advanced fibrosis/cirrhosis (F3/F4)	41.1	14.1	<0.001

* Data are presented as median (interquartile range) or % of patients.

Results

In total, 284 patients (142 with HBsAg loss and 142 without HBsAg loss), matched for sex (51.4% male), were included in the analysis (Table). Despite efforts to match for age, the baseline age was higher in patients with HBsAg loss than in patients without HBsAg loss (60 vs 55.7 years, P<0.001). A higher percentage of patients with HBsAg loss had ELF-defined advanced fibrosis or cirrhosis (F3/F4) [41.1% vs 14.1%, P<0.001]. However, LS-defined F3/F4 was present in <5% of patients in both groups.

Overall, 1.8% of patients with CHB demonstrated fibrosis regression at 3 years when both ELF and LS criteria were applied (1.4% in patients with HBsAg loss vs 2.1% in patients without HBsAg loss, P=1.000). When only the ELF criteria were applied, 14.5% of patients with HBsAg loss and 16.9% of patients without HBsAg loss showed fibrosis regression at 3 years (Fig).

Compared with the age at HBsAg loss of >50 years, the age at HBsAg loss of <50 years was associated with lower prevalences of ELF-defined F3/F4 at baseline (5.9% vs 52.3%, P<0.001) and 3 years (20.6% vs 63.8%, P<0.001), as well as lower prevalences of LS-defined F3/F4 at baseline (2.9% vs 5.6%, P=1.000) and 3 years (3.0% vs 13.9%, P=0.118).

Discussion

HBsAg loss is considered a clinical endpoint of functional cure in CHB, associated with lower risks of HCC and decompensated liver disease. In our study, only 1.4% of patients with HBsAg loss showed fibrosis regression at 3 years when both ELF and LS criteria were applied. Using only the ELF criteria, 14.5% of patients with HBsAg loss exhibited fibrosis regression at 3 years. Outcomes were similar between patients with and without HBsAg loss. Our hypothesis that HBsAg loss would be associated with fibrosis regression was not supported, possibly due to the higher mean age among patients with HBsAg loss. Despite the finding of HBsAg loss, these patients remain at risk for advanced fibrosis and cirrhosis-related complications.

The low percentage of patients with fibrosis regression may be related to the protocol-defined endpoint of fibrosis regression, which required meeting both LS and ELF criteria. At baseline, 95.8% of patients had LS values indicative of F0/F1 or grey zone. The ELF criteria are more sensitive than LS criteria in patients with an apparently low risk of liver complications (normal ALT, treatment-naïve); half of our patients had already achieved functional cure.

Age at HBsAg loss of <50 years was associated with a lower prevalence of ELF-defined F3/F4 at baseline, compared with the age at HBsAg loss of >50 years (5.9% vs. 52.3%, P<0.001). These findings confirm that the benefits of HBsAg seroclearance are most prominent when it occurs before age 50 years.[1] Nonetheless, patients can exhibit F3/F4 despite achieving HBsAg seroclearance, especially if the seroclearance occurs after age 50 years. Ongoing surveillance for liver-related complications is recommended for these patients.

Metabolic factors, including overweight and type 2 diabetes, were present in a high percentage of patients with HBsAg loss (56.3% and 17.6%, respectively) and may have contributed to the high prevalence (41.1%) of ELF-defined F3/F4 at baseline.

Limitations of the present study included its lack of liver biopsy for histological assessment of liver fibrosis and its short follow-up period. Strengths of the study included its prospective design, the use of a combination of non-invasive assessments for liver fibrosis, and the inclusion of a homogenous population.

Conclusion

Although a longer duration of HBsAg loss was associated with a higher likelihood of fibrosis regression, the effects were influenced by age. Age at HBsAg loss has prognostic implications for advanced fibrosis and cirrhosis risks. Patients achieving HBsAg seroclearance after age 50 years should receive ongoing surveillance for liver-related complications. Novel treatments to induce functional cure in CHB patients should target younger populations, who have greater potential for clinical improvement.

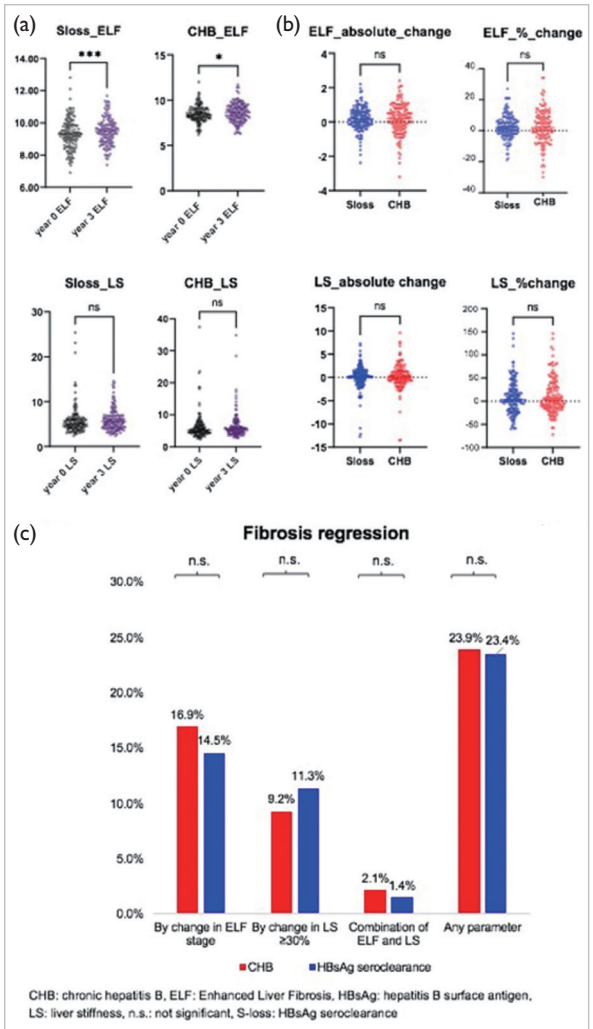


FIG. Comparisons between patients with and without hepatitis B surface antigen (HBsAg) loss in terms of (a) median Enhanced Liver Fibrosis (ELF) test and liver stiffness (LS) values at baseline and 3 years, (b) median absolute and percentage changes in ELF and LS values at 3 years, and (c) percentages of patients achieving fibrosis regression at 3 years based on various criteria.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#16171251). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Mak LY, Hui RW, Chung MSH, et al. Regression of liver fibrosis after HBsAg loss: a prospective matched case-control evaluation using transient elastography and serum enhanced liver fibrosis test. J Gastroenterol Hepatol 2024. doi:10.1111/jgh.16728

Acknowledgements

We thank Ms Delanda Wong and Mr John Yuen for their assistance in participant recruitment.

References

1. Yuen MF, Wong DK, Fung J, et al. HBsAg seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. Gastroenterology 2008;135:1192-9.
2. European Association for Study of Liver, Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237-64.
3. Papastergiou V, Tsochatzis E, Burroughs AK. Non-invasive assessment of liver fibrosis. Ann Gastroenterol 2012;25:218-31.
4. Mak LY, Seto WK, Hui RW, et al. Fibrosis evolution in chronic hepatitis B e antigen-negative patients across a 10-year interval. J Viral Hepat 2019;26:818-27.
5. Martinez SM, Fernandez-Varo G, Gonzalez P, et al. Assessment of liver fibrosis before and after antiviral therapy by different serum marker panels in patients with chronic hepatitis C. Aliment Pharmacol Ther 2011;33:138-48.

Squalene epoxidase as a novel therapeutic target in non-alcoholic fatty liver disease: abridged secondary publication

D Liu, CC Wong, J Yu *

KEY MESSAGES

1. Squalene epoxidase (SQLE), a key enzyme in cholesterol biosynthesis, is upregulated in non-alcoholic fatty liver disease (NAFLD).
2. Liver-specific SQLE overexpression in mice induces spontaneous onset of steatosis and accelerates NAFLD progression in dietary models.
3. The SQLE inhibitor terbinafine suppresses NALFD development in both dietary and genetic mouse models.
4. Serum SQLE is a potential diagnostic biomarker for NAFLD.

Hong Kong Med J 2024;30(Suppl 7):S40-5
HMRF project number: 07181256

D Liu, CC Wong, J Yu

Institute of Digestive Disease and Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China

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

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of liver disease and a substantial healthcare burden worldwide. NAFLD encompasses a spectrum of liver pathologies, ranging from steatosis to non-alcoholic steatohepatitis (NASH).[1] The latter is an aggressive form of NAFLD associated with hepatocellular injury and inflammation; it can progress to fibrosis, cirrhosis, and eventually hepatocellular carcinoma.[2] Although steatosis can be reversed by lifestyle modifications, NASH often causes irreversible damage such as cirrhosis. Dysregulated hepatic metabolism can cause steatosis and progression to NASH. Thus, hepatic metabolic pathways have been targeted to suppress NAFLD progression or promote NASH resolution. Cholesterol, a major lipotoxic molecule, plays a central role in NASH pathogenesis.[3] Squalene epoxidase (SQLE) is a rate-limiting enzyme in the endogenous cholesterol biosynthesis pathway and an aetiological factor in both NAFLD and hepatocellular carcinoma.[4] We therefore hypothesise that SQLE serves important roles in the development of NAFLD and NASH.

In this study, we demonstrated that SQLE is upregulated in patients with NAFLD. Liver-specific *Sqle* overexpression in mice led to spontaneous steatosis and exacerbated high-fat, high-cholesterol (HFHC) diet–induced NASH in mice. In contrast, Sqle knockout (ko) mice exhibited less severe NAFLD and NASH. Pharmacological inhibition of SQLE via terbinafine ameliorated NASH in multiple mouse models. Moreover, serum SQLE could serve as a novel biomarker for diagnoses of NAFLD and NASH.

Methods

The role of SQLE in NAFLD development was examined using hepatocyte-specific Sqle transgenic (tg) mice. Mice were fed various diets to induce NAFLD including an HFHC diet and a methionine- and choline-deficient diet. To target SQLE, we repurposed terbinafine, a Food and Drug Administration–approved SQLE inhibitor, for NAFLD treatment in multiple mouse models. Serum SQLE levels were compared between a cohort of patients with NAFLD and a cohort of healthy controls to assess its diagnostic performance on NALFD and NASH.

Results

Hepatocyte-specific *Sqle* overexpression in mice accelerates diet-induced NASH

Sqle tg mice and wildtype mice were fed an HFHC diet for 28 weeks to induce NASH. The HFHC diet increased both body and liver weight in wildtype mice; these effects were exacerbated in *Sqle* tg mice (Fig 1a). Liver and serum cholesterol and triglyceride levels were significantly increased in HFHC diet–fed *Sqle* tg mice (Fig 1b and 1c). Insulin and glucose tolerance tests revealed marked insulin resistance in HFHC diet–fed *Sqle* tg mice compared with wildtype mice (Fig 1c). Serum levels of alanine transaminase (ALT) and aspartate transaminase (AST) (Fig 1d) were significantly increased, along with levels of liver thiobarbituric acid reactive substances (TBARS), indicating liver damage and oxidative stress in HFHC diet–fed *Sqle* tg mice. Haematoxylin and eosin staining showed that HFHC diet–fed *Sqle* tg mice developed steatohepatitis with increased

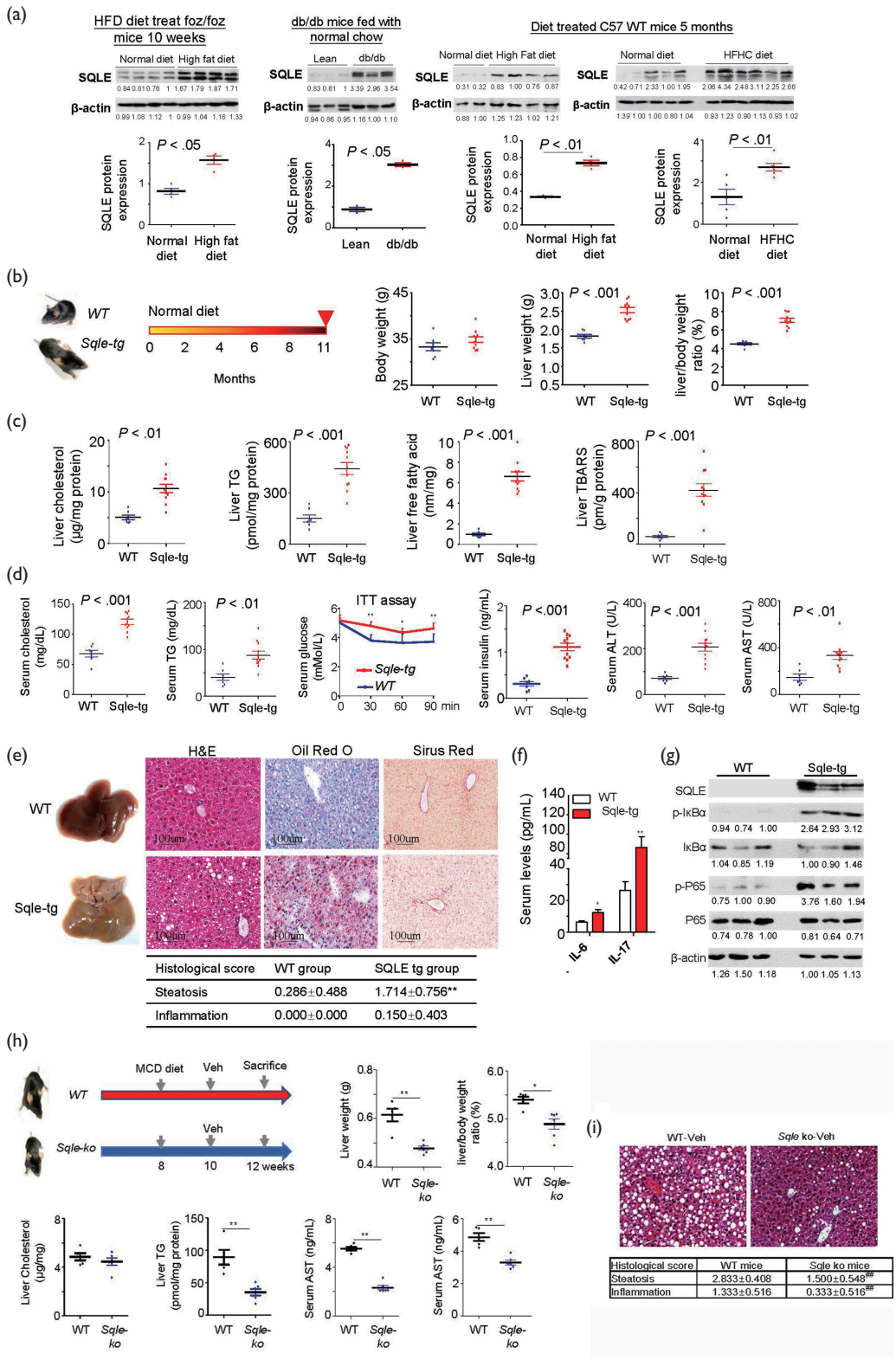


FIG 1. Diet-induced overexpression of liver squalene epoxidase (Sqle) in mice triggers spontaneous non-alcoholic fatty liver disease (NAFLD).
(a) Liver SQLE expression is upregulated in both dietary and genetic mouse models of non-alcoholic steatohepatitis (NASH). Hepatocyte-specific *Sqle* overexpression in mice induces spontaneous liver steatosis. Comparing standard chow–fed hepatocyte-specific *Sqle* tg and wildtype mice, (b) *Sqle* overexpression increases liver weight and liver/body weight ratio, without affecting body weight. (c) *Sqle* tg mice exhibit higher levels of liver cholesterol, triglycerides, free fatty acids, and thiobarbituric acid reactive substances (TBARS). (d) *Sqle* tg mice exhibit significantly elevated serum levels of cholesterol, triglycerides, alanine transaminase (ALT), and aspartate transaminase (AST), as well as enhanced insulin resistance. (e) Histological analyses, including haematoxylin and eosin (H&E) staining, Oil Red O staining, and Sirius red staining, reveal significantly increased steatosis and inflammation scores in livers of *Sqle* tg mice, compared with wildtype mice. (f) *Sqle* tg mice exhibit significantly elevated serum levels of IL-6 and IL-17, compared with wildtype mice. (g) Western blot analysis shows increased hepatic expression of p-P65 and p-IκBα in *Sqle* tg mice. In hepatocyte-specific *Sqle* ko mice fed a methionine- and choline-deficient diet, (h) *Sqle* ko mice show decreases in liver weight, liver/body weight ratio, liver cholesterol and triglyceride levels, and serum levels of ALT and AST compared with wildtype mice. (i) Haematoxylin and eosin staining demonstrates lower steatosis and inflammation scores in *Sqle* ko mice.

steatosis (P<0.01) and inflammation (P<0.01) scores, compared with HFHC diet–fed wildtype mice. This observation was confirmed by hepatic lipid accumulation and the presence of fibrosis according to Sirius red staining (Fig 1e). Consistent with a role for Sqle in NASH induction, serum cytokine and chemokine assays revealed elevated levels of pro-inflammatory cytokines (eg, IL-1β, IL-6, MCP-1, MIP-1β, and TNF-α) in *Sqle* tg mice (Fig 1f). NF-κB pathway activation was observed in *Sqle* tg mice, as evidenced by increased levels of p-Iκbα and p-p65 (Fig 1g). These findings suggest that Sqle accelerates NASH progression in the context of an HFHC diet.

Hepatocyte-specific *Sqle* knockout in mice inhibits diet-induced NASH

We constructed hepatocyte-specific *Sqle* ko mice and then fed both *Sqle* ko mice and their wildtype littermates a methionine- and choline-deficient diet for 8 weeks. *Sqle* ko mice displayed decreases in body weight, liver/body weight ratio, liver cholesterol and triglyceride levels, and serum levels of ALT and AST (Fig 1h). *Sqle* ko mice fed a methionine- and choline-deficient diet also developed less severe steatohepatitis, as evidenced by decreased steatosis (P<0.01) and inflammation (P<0.01) scores (Fig 1i). Taken together, these results suggest that the absence of Sqle attenuates diet-induced NASH.

Pharmacological inhibition of Sqle ameliorated NASH in Sqle tg mice

Terbinafine is an SQLE inhibitor for treatment of fungal infections. To evaluate the utility of SQLE as a therapeutic target for NAFLD/NASH, we administered terbinafine (80 mg/kg/d) to HFHC diet–fed *Sqle* tg mice at 26 weeks after HFHC diet initiation until week 34. Terbinafine reversed the *Sqle* tg-associated increase in liver/body weight ratio (Fig 2a). Terbinafine also abolished *Sqle* tg-induced accumulation of liver cholesterol, triglycerides, and free fatty acids (Fig 2b), as well as serum levels of cholesterol and triglycerides (Fig 2c). Furthermore, terbinafine normalised insulin sensitivity, as evidenced by insulin tolerance test results and serum insulin levels. In addition to the alleviation of steatosis, terbinafine lowered serum levels of ALT and AST (Fig 2c), as well as levels of liver TBARS (Fig 2b), indicating the reversal of Sqle-induced liver damage and oxidative stress. Histological evaluation confirmed that terbinafine significantly attenuated the severities of steatohepatitis, lipid accumulation, and fibrosis (Fig 2d). Consistent with these mitigating effects on steatohepatitis, terbinafine-treated *Sqle* tg mice showed reduced levels of serum pro-inflammatory cytokines including IL-1β, IL-6, MCP-1, and TNF-α (Fig 2e), as well as suppressed NF-κB activation (p-Iκbα and p-p65) [Fig 2f]. No obvious toxicity was observed during terbinafine treatment in mice. These results collectively suggest that SQLE targeting can be a treatment modality for NASH.

Pharmacological inhibition of SQLE ameliorated NASH development in wildtype mice

We evaluated the efficacy of terbinafine (80 mg/kg) in mitigating HFHC diet–induced NASH in wildtype mice. Treatment was initiated at 26 weeks after HFHC diet initiation and continued until week 32. Terbinafine significantly reduced liver weight and liver/body weight ratio (Fig 3a). It also abolished HFHC diet–induced accumulation of liver triglycerides and free fatty acids (Fig 3b) and lowered serum triglyceride levels (Fig 3c), while improving insulin and glucose tolerance. Moreover, better control of liver damage was confirmed by decreases in liver TBARS levels (Fig 3b) and levels of serum ALT and AST (Fig 3c). Histological evaluation confirmed that terbinafine attenuated steatohepatitis, lipid accumulation, and liver fibrosis, as evidenced by lower steatosis and inflammation scores (Fig 3d). Consistent with these findings, terbinafine suppressed serum pro-inflammatory cytokines (Fig 3e), indicating its effectiveness in reducing HFHC diet–induced liver inflammation. Overall, SQLE targeting confers therapeutic benefits in HFHC diet–induced NASH.

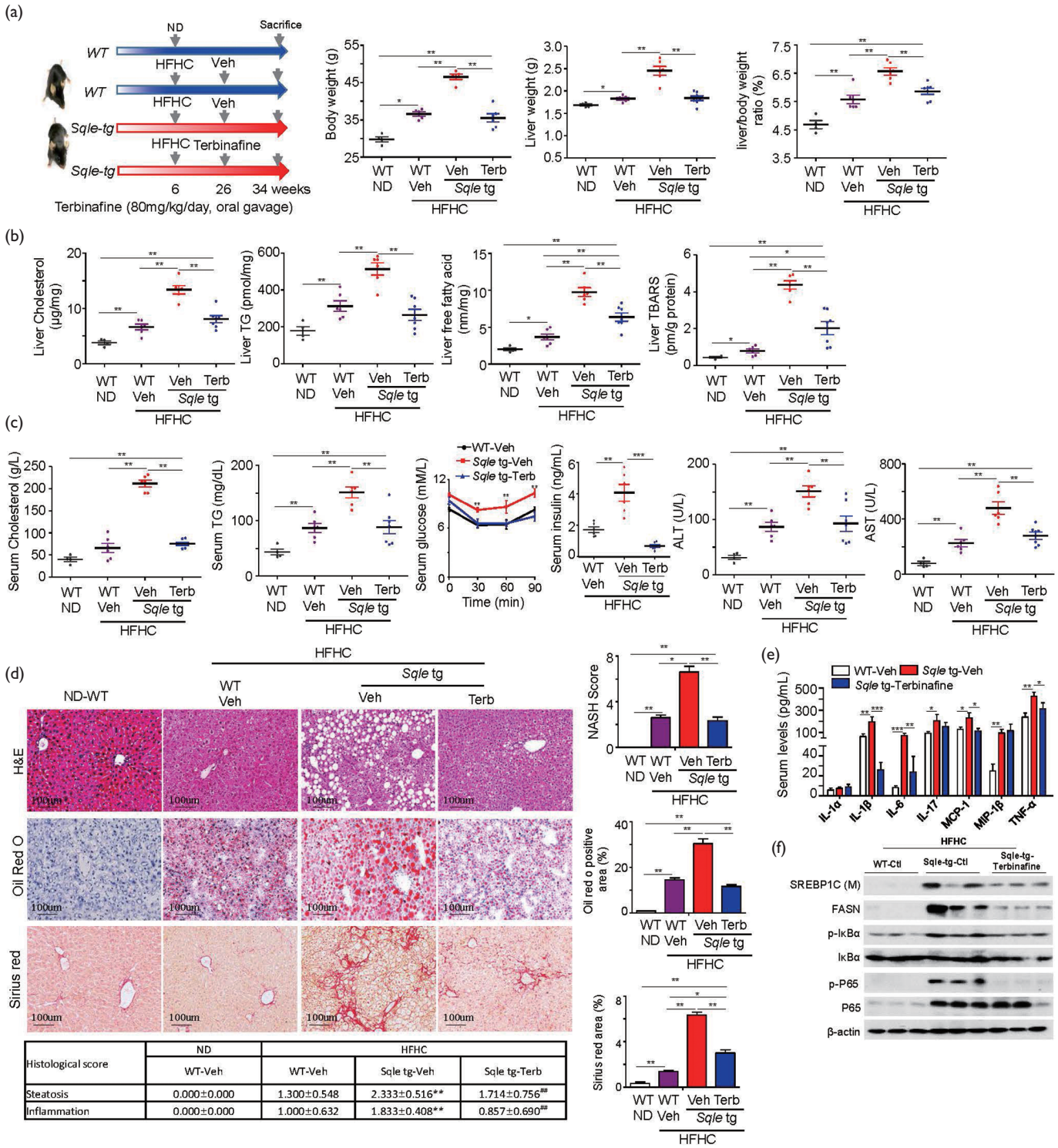
SQLE is a potential diagnostic biomarker for NAFLD and NASH

We measured serum SQLE levels in 829 individuals across four patient cohorts. The area under the receiver operating characteristic curve was 0.602 for distinguishing patients with NAFLD from healthy controls, 0.628 for distinguishing patients with NASH from healthy controls, and 0.611 for distinguishing patients with NASH from patients with steatosis (Fig 3f). Thus, serum SQLE can be a diagnostic biomarker for NAFLD and NASH.

Discussion

Our findings indicate that SQLE plays a pivotal role in NAFLD development. Hepatocyte-specific *Sqle* overexpression in mice led to spontaneous steatosis and exacerbated diet-induced NASH. SQLE increases cholesterol and triglyceride levels in hepatocytes, while activating pro-inflammatory signalling. Pharmacological inhibition of SQLE ameliorated NASH in experimental mouse models, suggesting that SQLE can be a therapeutic target for NASH.

High dietary cholesterol can induce NASH in mouse models,[5] although the role of the cholesterol biosynthetic pathway in NASH pathogenesis remains unclear. In the present study, we demonstrated a causative role for SQLE in NASH using hepatocyte-specific *Sqle*-overexpressing transgenic mice (*Sqle* tg).



Histological score	ND	HFHC		
	WT-Veh	WT-Veh	Sqle tg-Veh	Sqle tg-Terb
Steatosis	0.000±0.000	1.300±0.548	2.333±0.516**	1.714±0.756##
Inflammation	0.000±0.000	1.000±0.632	1.833±0.408**	0.857±0.690##

FIG 2. Pharmacological inhibition of Sqle ameliorated NASH in mice: in HFHC-fed *Sqle* tg mice treated with terbinafine, (a) terbinafine reverses *Sqle* tg–associated increases in body weight, liver weight, and liver/body weight ratio. (b) Terbinafine abolishes hepatic *Sqle* expression–induced levels of liver cholesterol, triglycerides, free fatty acids, and thiobarbituric acid reactive substances (TBARS), as well as (c) serum levels of cholesterol, triglycerides, alanine transaminase (ALT), and aspartate transaminase (AST), along with insulin resistance. Histological analyses using haematoxylin and eosin staining, Oil Red O staining, and Sirius red staining of wildtype and *Sqle* tg mouse livers demonstrate that terbinafine significantly attenuated (d) the severities of steatohepatitis, lipid accumulation, and fibrosis, as well as (e) serum levels of IL-1βIL-6, MCP-1, and TNF-α in vehicle and terbinafine-treated livers. (f) Western blot analysis shows that terbinafine suppressed SQLE-induced protein expression of Srebp1c, Fasn, p-P65, and p-IκBα.

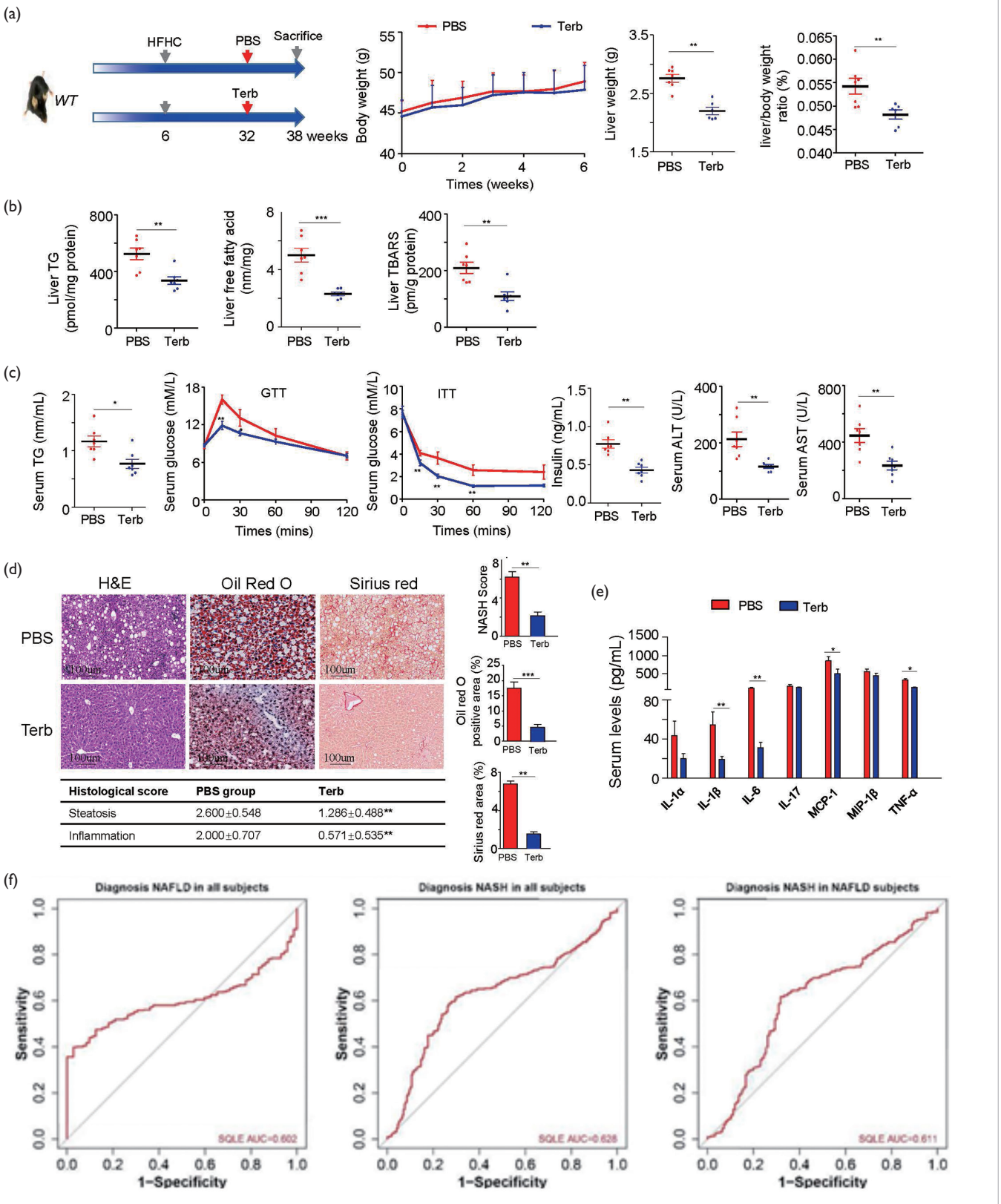


FIG 3. Pharmacological inhibition of SQLE ameliorated NASH in wild type mice. In mice with HFHC diet–induced NASH treated with terbinafine, (a) terbinafine significantly reduces liver weight and liver-to-body weight ratio. (b) Terbinafine abolishes HFHC diet–induced accumulation of liver triglycerides, free fatty acids, and thiobarbituric acid reactive substances (TBARS), as well as (c) serum triglycerides, alanine transaminase (ALT), and aspartate transaminase (AST), while improving insulin and glucose tolerance. (d) Liver histology analyses indicate that terbinafine attenuated steatohepatitis, lipid accumulation, and liver fibrosis, as well as (e) serum levels of IL-1α, IL-1β, IL-6, IL-17, MCP-1, MIP-1β, and TNF-α. (f) Diagnostic performance of serum SQLE in distinguishing patients with NAFLD from healthy controls, patients with NASH from healthy controls, and patients with NASH from patients with NAFLD.

On a standard diet, *Sqle* tg mice developed hypercholesterolaemia, hyperlipidaemia, spontaneous hepatic steatosis, and liver damage. When fed an HFHC diet, *Sqle* tg mice exhibited rapid development of NASH with increased inflammation and fibrosis, compared with wildtype mice. In contrast, *Sqle* ko mice exhibited alleviation of NAFLD and NASH development. Collectively, our data suggest that SQLE plays a functional role in the initiation of hepatic steatosis and its progression to NASH.

No drug has been approved for the treatment of NASH. In our study, we found that terbinafine ameliorated NASH in multiple mouse models. This effect is likely due to the inhibition of cholesterol and lipid biosynthesis, thereby suppressing the major causative metabolic pathways involved in NASH. No apparent toxicity was observed during terbinafine treatment. Targeting SQLE is a promising approach for the prevention and treatment of NASH.

Serum SQLE showed good diagnostic performance in distinguishing patients with NALFD or NASH from healthy controls, and patients with NASH from patients with steatosis. Thus, SQLE is a promising diagnostic biomarker for NALFD and NASH.

Conclusion

SQLE is a pivotal gene in the initiation and progression of NASH. It is involved in cholesterol biosynthesis, de novo lipogenesis, and inflammation. Targeting SQLE confers a therapeutic benefit in animal models. Serum SQLE is a diagnostic biomarker for NASH.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#07181256). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Liu D, Wong CC, Zhou Y, et al. Squalene epoxidase induces nonalcoholic steatohepatitis via binding to carbonic anhydrase III and is a therapeutic target. Gastroenterology 2021;160:2467-82.e3.
2. Wang F, Zhang X, Liu W, et al. Activated natural killer cell promotes non-alcoholic steatohepatitis through mediating JAK/STAT pathway. Cell Mol Gastroenterol Hepatol 2022;13:257-74.
3. Li C, Wang Y, Liu D, et al. Squalene epoxidase drives cancer cell proliferation and promotes gut dysbiosis to accelerate colorectal carcinogenesis. Gut 2022;71:2253-65.

References

1. Schuppan D, Schattenberg JM. Non-alcoholic steatohepatitis: pathogenesis and novel therapeutic approaches. J Gastroenterol Hepatol 2013;28(Suppl 1):68-76.
2. Yu J, Shen J, Sun TT, Zhang X, Wong N. Obesity, insulin resistance, NASH and hepatocellular carcinoma. Semin Cancer Biol 2013;23:483-91.
3. Ioannou GN. The role of cholesterol in the pathogenesis of NASH. Trends Endocrinol Metab 2016;27:84-95.
4. Liu D, Wong CC, Fu L, et al. Squalene epoxidase drives NAFLD-induced hepatocellular carcinoma and is a pharmaceutical target. Sci Transl Med 2018;10:eaap9840.
5. Liang JQ, Teoh N, Xu L, et al. Dietary cholesterol promotes steatohepatitis related hepatocellular carcinoma through dysregulated metabolism and calcium signaling. Nat Commun 2018;9:4490.

Retinal imaging to identify patients with atrial fibrillation at increased risk of intracerebral haemorrhage: abridged secondary publication

Y Soo, C Cheung, D Yang, J Abrigo, B Lam, H Zheng, SF Tsang, B Ip, W Chu, V Mok, T Leung *

KEY MESSAGES

1. In patients with atrial fibrillation receiving oral anticoagulants for stroke prevention, there is an increasing incidence of anticoagulant-associated intracerebral haemorrhage, which carries high risks of morbidity and mortality.
2. The presence of cerebral microbleeds (CMBs) on magnetic resonance imaging (MRI) of the brain is associated with an increased risk of intracerebral haemorrhage.
3. The retina shares an embryological origin and similar pathological characteristics with the brain; thus, changes in retinal vessels may indicate the presence of CMBs. A non-invasive method to evaluate bleeding-prone cerebral small vessel disease in patients with atrial fibrillation could help to identify those at increased risk of anticoagulant-associated intracerebral haemorrhage.
4. We recruited patients with atrial fibrillation to undergo optical coherence tomography-angiography (OCT-A) for examination of the three-dimensional capillary network of the retina. We compared capillary network matrix parameters between patients with and without CMBs on MRI.
5. Alterations in the retinal capillary network across various retina layers were associated with the presence and burden of CMBs on MRI. These findings suggest a role for OCT-A in identifying patients with atrial fibrillation at increased risk of bleeding-prone microangiopathy.

Hong Kong Med J 2024;30(Suppl 7):S46-7
HMRF project number: 06171106

[1] Y Soo, [2] C Cheung, [2] D Yang, [3] J Abrigo, [1,4,5] B Lam, [1,4,5] H Zheng, [1] SF Tsang, [1] B Ip, [3] W Chu, [1,4,5] V Mok, [1] T Leung

[1] *Division of Neurology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China*
[2] *Department of Ophthalmology and Visual Sciences, Hong Kong Eye Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China*
[3] *Department of Imaging and Interventional Radiology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong SAR, China*
[4] *Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China*
[5] *Nuffield Department of Clinical Neurosciences, Wellcome Centre for Integrative Neuroimaging, University of Oxford, United Kingdom*

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

Introduction

Atrial fibrillation (AF) causes one-third of ischaemic strokes, which have high morbidity and mortality.[1] Oral anticoagulants are effective in reducing the risk of ischaemic stroke by 60% to 70%, but the risk of intracerebral haemorrhage remains, particularly in patients with multiple cerebral microbleeds (CMBs) visible on magnetic resonance imaging (MRI) of the brain.[2] Access to MRI is limited among patients with AF who have no history of stroke or transient ischaemic attacks. Furthermore, many patients with AF have contraindications for MRI (eg, cognitive impairment, severe disability after stroke, or the presence of a pacemaker and/or metallic heart valve). A non-invasive method to evaluate bleeding-prone cerebral small vessel disease in patients with AF could help to customise treatment decisions. The retina shares embryological and anatomical features with the brain; thus, many pathological changes in cerebral vessels are reflected in retinal vessels.[3] Optical coherence tomography-angiography (OCT-A) is a non-invasive technique for visualising the microvasculature of the retina and choroid; it provides three-dimensional images of capillary networks in the eye without requiring intravenous dye injection.[4] Using semi-automated computer software, vascular parameters in different retinal layers can be precisely quantified for analysis. This study aimed to identify changes in retinal vascular parameters on OCT-A that are associated with the presence of CMBs on MRI of the brain among patients with AF.

Methods

Between November 2018 and January 2022, Chinese patients aged ≥18 years with AF or atrial flutter were prospectively recruited from outpatient clinics at Prince of Wales Hospital. Patients were excluded if they had contraindications for MRI of the brain (eg, presence of a pacemaker or metallic heart

valve), poor sitting balance for retinal photography, known intracranial or ocular pathologies, or were pregnant. Additionally, healthy controls aged ≥60 years were recruited from the community. OCT-A was performed within 2 weeks of MRI of the brain.

To determine associations between changes in OTC-A metrics and the longitudinal progression of CMB count, a subgroup of patients with prior MRI from the IPAAC (risk of Intracerebral haemorrhage in Patients taking oral Anticoagulants for Atrial fibrillation with Cerebral microbleeds) study was identified.[5] The CMB counts in the two sets of MRIs were compared to identify new CMB development. OCT-A metrics were compared between patients with and without new CMBs in the follow-up MRI.

Results

Of 135 patients with AF and 65 healthy controls recruited, 99 patients with AF and 60 healthy controls were included in the analysis. Multivariable logistic regression models showed that in both groups changes in the retinal capillary matrix were associated with the presence and burden of CMBs in the superficial capillary plexus, deep capillary plexus, and disc centre, after adjustment for confounders. Among patients with previous MRI of the brain from the IPAAC study, those with new CMBs on follow-up MRI had similar changes on OCT-A.

Discussion

To our knowledge, this is the first study to evaluate associations between retinal capillary network changes and CMBs in patients with AF. Although the exact mechanism underlying these vascular changes remains uncertain, we hypothesise that it involves capillary drop-out and secondary vasodilatation at the capillary layer.

This study was limited by disruptions due to the COVID-19 pandemic and social unrest in Hong Kong, which resulted in more than one-third of patients to have a >2-week interval between retinal imaging and MRI. Although the difference was not significant between patients with and without CMBs, the analysis was adjusted for this confounder.

Conclusions

OCT-A has a role in identifying patients at increased risk of anticoagulant-associated intracerebral haemorrhage. Further studies with larger sample size are needed to determine cut-off values for OCT-A parameters.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#06171106). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

References

1. Ip B, Au L, Chan A, et al. Evolving ischemic stroke subtypes in 15 years: a hospital-based observational study. Int J Stroke 2022;17:444-54.
2. Charidimou A, Karayiannis C, Song TJ, et al. Brain microbleeds, anticoagulation, and hemorrhage risk: meta-analysis in stroke patients with AF. Neurology 2017;89:2317-26.
3. Goto I, Katsuki S, Ikui H, Kimoto K, Mimatsu T. Pathological studies on the intracerebral and retinal arteries in cerebrovascular and noncerebrovascular diseases. Stroke 1975;6:263-9.
4. Spaide RF, Klancnik JM Jr, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. JAMA Ophthalmol 2015;133:45-50.
5. Soo Y, Abrigo JM, Leung KT, et al. Risk of intracerebral haemorrhage in Chinese patients with atrial fibrillation on warfarin with cerebral microbleeds: the IPAAC-Warfarin study. J Neurol Neurosurg Psychiatry 2019;90:428-35.

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