SUPPLEMENT 1

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Health and Medical Research Fund

Research Dissemination Reports

醫療衞生研究基金

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HONG KONG MEDICAL JOURNAL 香港醫學雜誌
Volume 32 Number 1 **February 2026**
SUPPLEMENT 1

Health and Medical Research Fund

Research Dissemination Reports

CANCER

CHILD AND ADOLESCENT HEALTH

Editorial

Dissemination reports are concise informative reports of health-related research supported by the Health and Medical Research Fund administered by the Health Bureau. In this edition, we present 12 dissemination reports of projects related to primary healthcare and preventive care, genomic medicine, rare diseases, non-communicable diseases, cancer, and child and adolescent health. In particular, research findings of three projects may provide insights to enhance clinical practices and help inform health policy formulation in Hong Kong.

Behavioural and pharmacological smoking cessation interventions can significantly increase the chances of successfully quitting. Despite free smoking cessation services being available in Hong Kong, few smokers have used or ever intend to use them. New modes of delivering smoking cessation interventions are required. Cheung et al[1] evaluated the feasibility and efficacy of an intervention comprising ecological momentary assessment (EMA) followed by nurse-led telephone counselling and text messaging, compared to no intervention after EMA, among over 450 adult current smokers. EMA is a self-administered documentation of real-time data describing behaviour, cognition, or event in the real world. All participants completed EMA assessments five times per day for seven days to document their smoking triggers, behaviours, and daily cigarette consumption. The intervention comprised nurse-led telephone counselling and 10-week tailored messages via instant messaging applications. The control group did not receive any intervention after the 1-week EMA. The results showed that EMA-based intervention was effective in increasing biochemically validated tobacco abstinence (from 3.5% to 8.2%) and smokers' readiness and preparation for quitting, compared to EMA alone, among smokers with no intention to use smoking cessation aids. Low-intensity EMA with personalised smoking cessation intervention could be a new and effective treatment model.

The adverse effects related to prolonged usage of electronic devices are a growing concern and have been linked to a range of physical and psychological symptoms, including mood disturbance, poor sleep quality, impaired academic performance, musculoskeletal pain, and vision problems. Tsang et al[2] aimed to enhance individual's knowledge and awareness of the health risks associated with prolonged usage of smart devices, and to educate and promote adoption of healthy habits with respect to smart device use among primary and secondary school students. The study found a high prevalence of self-reported musculoskeletal, vision, and psychosocial symptoms among adolescents with excessive usage of electronic devices. There was moderate association between the intensity of electronic device usage and musculoskeletal, vision, and psychosocial symptoms. Frequent breaks, physical activity, and focus-group programmes incorporating motivational interviewing to explore and formulate strategies to promote healthier usage habits may help reduce the negative impacts associated with excessive or problematic use of electronic devices.

Asthma and attention-deficit hyperactivity disorder (ADHD) are prevalent chronic paediatric conditions. Children with early childhood asthma are more likely to develop ADHD. Acceptance and commitment therapy (ACT) is a mindfulness-based cognitive-behavioural technique, which has shown benefits in reducing behavioural issues in children with various conditions. Chong et al[3] investigated the effects and cost-effectiveness of an ACT-based asthma management programme, compared to treatment-as-usual, on health outcomes in 118 children aged 3 to 12 years with asthma and comorbid ADHD, as well as in their parents. The results showed a substantial reduction in unplanned healthcare visits and significant improvement in asthma control and ADHD symptom severity at 12 months post-intervention. Parents also experienced improvements in psychological adjustment, asthma management self-efficacy, psychological flexibility, parenting competence, and overall family functioning across the 12-month follow-up period. Compared with baseline, the ACT group avoided 38 hospital/clinic visits, whereas the treatment-as-usual group experienced 22 additional visits. The incremental cost-effectiveness ratio was HK$913 per visit avoided. The high recruitment and retention rates observed in this study indicate the ACT programme's feasibility and acceptance.

Supplement editors

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References

1. Cheung YTD, Lam TH, Ho SY, Wang MP, Chan CHH. Ecological momentary assessment for smoking cessation: abridged secondary publication. Hong Kong Med J 2026;32(Suppl 1):S4-6.
2. Tsang SMH, Cheing GLY, Lam AKC, et al. Health-conscious programme for appropriate use of smart devices: abridged secondary publication. Hong Kong Med J 2026;32(Suppl 1):S7-11.
3. Chong YY, Chien WT, Fung K, Poon CHA, Leung SP, Lam SY. Acceptance and commitment therapy–based asthma management programme for parents of children with asthma and attention-deficit hyperactivity disorder: abridged secondary publication. Hong Kong Med J 2026;32(Suppl 1):S37-42.

Ecological momentary assessment for smoking cessation: abridged secondary publication

YTD Cheung *, TH Lam, SY Ho, MP Wang, CHH Chan

KEY MESSAGE

Among smokers with no intention to use smoking cessation aids, ecological momentary assessment (EMA), followed by nurse-led phone counselling and text messaging, was effective in increasing tobacco abstinence and smokers' readiness and preparation for quitting, relative to no intervention after EMA completion.

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Introduction

Smoking is the leading modifiable risk factor for premature death.[1] Behavioural and pharmacological interventions can double the chance of successful smoking cessation.[2] However, unassisted quitting remains widely used.[3] In 2017, among Hong Kong smokers, 81.2% were aware of free smoking cessation services; however, only 2.6% and 4.0% had ever used and intended to use these services, respectively.[4]

Ecological momentary assessment (EMA) is self-administered documentation of behaviours, cognitions, and events. It can reduce bias in reporting negative behaviours, while facilitating analysis of temporal and causal relationships between event exposures and smoking-related outcomes.[5] EMA can be used to monitor smoking characteristics and customise cessation treatment. Smokers who are not ready to quit might not proactively seek smoking cessation aids. They may be more interested in monitoring their smoking behaviours and receiving personalised quitting support. This study aimed to evaluate the efficacy of an EMA-based smoking cessation intervention.

Methods

This two-arm, open-labelled, randomised controlled trial was conducted between March 2022 and January 2023. Individuals were eligible if they were aged ≥18 years, had smoked daily in the preceding 7 days—verified by exhaled carbon monoxide (≥4 parts per million) or salivary cotinine (≥30 ng/mL), had no intention to use smoking cessation services or medications in the coming month, and had not used any such services or medications in the preceding 7 days. Individuals who were pregnant or diagnosed with mental illness were excluded.

Participants were instructed to document their smoking triggers (withdrawal, emotional, social, and habitual), smoking behaviours (smoking, nicotine craving, and tobacco product purchasing), and daily cigarette consumption five times (at 3-hour intervals) per day during waking hours for 1 week using the Smoking Radar App. Subsequently, participants were randomly assigned to receive no intervention or personalised smoking cessation intervention (including nurse-led phone counselling and 10-week customised messages via instant messaging applications) guided by the EMA information. In total, 31 text messages were sent on a tapering schedule, from eight in the first week to one in the tenth week. Core messages included a summary of the 1-week EMA, the harmful effects of smoking, the benefits of quitting, methods to cope with nicotine withdrawal symptoms, and the quit plan. Additional messages addressing coping strategies for personal smoking triggers were also provided.

At the 3-month follow-up, participants were assessed for behavioural progression toward smoking cessation using the Incremental Behaviour Change Toward Smoking Cessation (IBC-S) [scores range from 0 to 24; higher scores indicate more readiness and preparation in quitting], tobacco abstinence in the past 7 days according to exhaled carbon monoxide (<4 parts per million) or salivary cotinine (<30 ng/mL), and self-reported use of smoking cessation services or medications. EMA compliance and satisfaction with the intervention were also assessed. Satisfaction was rated on a scale ranging from 0 (very dissatisfied) to 4 (very satisfied).

An intention-to-treat analysis was performed by assuming that non-respondents at the 3-month follow-up were smokers. Logistic and linear regression analyses were conducted to assess the effect of the personalised intervention on IBC-S scores.

Results

Of 1461 individuals screened, 1179 were eligible; 459 of them (mean age, 36.7±10.7 years; 33.8% women) were randomly assigned to the intervention (n=231) or control (n=228) group. The retention rate was 89.8% at the 3-month follow-up and did not significantly differ between groups. The two groups were comparable, except that the intervention group had higher scores for perceived importance of quitting and perceived confidence in quitting (Table 1).

At the 3-month follow-up, the intervention group had a higher tobacco abstinence rate (odds ratio [OR]=2.46, P=0.04), higher IBC-S scores (unstandardised B=0.84, P<0.01), greater use of smoking cessation services (OR=7.72, P<0.001), and greater use of smoking cessation medications (OR=5.83, P<0.001) [Table 2].

EMA compliance rates were 73.9% in the intervention group and 76.7% in the control group. Only 10 participants did not complete the 1-week EMA. Satisfaction scores were 2.9 for phone counselling and 2.8 for the 10-week text messaging programme (Table 3).

Discussion

At the 3-month follow-up, the EMA-based personalised intervention doubled the tobacco abstinence rate and increased smokers' readiness and preparation for quitting. The intervention also increased the use of smoking cessation services and medications, with a larger effect size. EMA was used to profile smoking characteristics, including tobacco consumption level, readiness to quit, withdrawal symptoms, tobacco purchasing, and smoking triggers. Guided by the EMA information, the intervention provided a more personalised quit plan to address specific smoking triggers; it also increased smokers' preparation to quit and acceptance of smoking cessation aids, while promoting subsequent initiation of abstinence.

This study has some limitations. Smokers with no intention to use smoking cessation services or medications were targeted; implementation of

TABLE 1. Characteristics of participants.

Characteristic	Intervention (n=231)*	Control (n=228)*
Age, y	36.0±10.5	37.4±10.9
Sex		
Male	147 (63.6)	157 (68.9)
Female	84 (36.4)	71 (31.1)
Education level		
Primary or below	3 (1.3)	1 (0.5)
Secondary	108 (46.7)	107 (46.9)
Post-secondary	120 (52.0)	120 (52.6)
Monthly household income, HK$	n=229	n=227
<30 000	113 (49.3)	119 (52.4)
30 000-59 999	85 (37.1)	79 (34.8)
≥60 000	31 (13.5)	29 (12.8)
No. of cigarettes per day	n=214	n=206
1-10	104 (48.6)	91 (44.2)
11-20	82 (38.3)	86 (41.7)
21-30	19 (8.9)	16 (7.8)
≥31	9 (4.2)	13 (6.3)
Nicotine dependence level, Heaviness of Smoking Index		
Low, 0-2	100 (43.3)	106 (46.5)
Moderate, 3-4	107 (46.3)	107 (46.9)
High, 5-6	24 (10.4)	15 (6.6)
Readiness to quit	n=230	
Within 30 days	35 (15.2)	28 (12.3)
Within 6 months	29 (12.6)	29 (12.7)
Over 6 months, not decided yet, or no	166 (72.2)	171 (75.0)
Incremental Behaviour Change Toward Smoking Cessation score	6.1±3.2	6.0±3.1
Previous quit attempts	n=230	
No	78 (33.9)	89 (39.0)
Yes	152 (66.1)	139 (61.0)
Self-efficacy		
Perceived importance of quitting	6.0±3.0	5.4±3.1
Perceived difficulty of quitting	7.2±2.7	7.1±2.8
Perceived confidence in quitting	4.9±2.4	4.4±2.7

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

TABLE 2. Outcomes at the 3-month follow-up.

Outcome	Intervention (n=231)*	Control (n=228)*	Crude odds ratio / unstandardised B (95% confidence interval)	P value
Biochemically validated tobacco abstinence	19 (8.2)	8 (3.5)	2.46 (1.06-5.75)	0.04
Incremental Behaviour Change Toward Smoking Cessation score	8.4±3.2	7.6±2.7	0.84 (0.30-1.38)	<0.01
Use of smoking cessation services	28 (12.1)	4 (1.8)	7.72 (2.62-22.40)	<0.001
Use of smoking cessation medication	36 (15.6)	7 (3.1)	5.83 (2.54-13.40)	<0.001

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

TABLE 3. Compliance and satisfaction with ecological momentary assessment–based smoking cessation intervention.

Outcome	Intervention	Control	P value
Compliance rate, %	73.9±23.8	76.7±21.8	0.19
Satisfaction			
Brief phone counselling (n=156)	2.9±0.6	-	-
10-week text messaging (n=190)	2.8±0.6	-	-

an EMA-based intervention for smokers who are already using smoking cessation services may not yield the same effect size. Additionally, the individual effects of EMA, brief phone counselling, and text messaging could not be disentangled. Future trials assessing the additive and interactive effects of the individual components are warranted. Only 3.1% of participants were aged ≥60 years, which is lower than the 8.1% among Hong Kong smokers, probably due to lower rates of smartphone use among older smokers.

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Disclosure

The results of this research have been previously published in:

1. Cheung YTD, Zhang MJ, Luk TT, Ho SY, Lam TH, Wang MP. Telephone counseling and messaging guided by mobile profiling of tobacco users for smoking cessation: a randomized clinical trial. JAMA Netw Open 2025;8:e250764.
2. Zhang MJ, He WJA, Luk TT, Wang MP, Chan SSC, Cheung YTD. Effectiveness of personalized smoking cessation intervention based on ecological momentary assessment for smokers who prefer unaided quitting: protocol for a randomized controlled trial. Front Public Health 2023;11:1147096.

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References

1. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med 2013;368:341-50.
2. World Health Organization. WHO report on the global tobacco epidemic, 2019: offer help to quit tobacco use. Accessed 1 April 2017. Available from: https://www.who.int/publications/i/item/9789241516204
3. Smith AL, Chapman S, Dunlop SM. What do we know about unassisted smoking cessation in Australia? A systematic review, 2005-2012. Tob Control 2015;24:18-27.
4. Census and Statistics Department, Hong Kong Special Administrative Region. Thematic Household Survey. Report No. 75: Internet and personal computer penetration. Pattern of Smoking. Accessed 1 April 2017. Available from: https://www.censtatd.gov.hk/en/data/stat_report/product/B1130201/att/B11302752022XXXXB0100.pdf
5. Shiffman S. Conceptualizing analyses of ecological momentary assessment data. Nicotine Tob Res 2014;16(Suppl 2):S76-S87.

Health-conscious programme for appropriate use of smart devices: abridged secondary publication

SMH Tsang *, GLY Cheing, AKC Lam, AMH Siu, PCK Pang, KC Yip, M Jensen

KEY MESSAGES

1. There is a high prevalence of self-reported musculoskeletal, visual, and psychosocial symptoms among adolescents with excessive use of electronic devices.
2. A moderate association was found between electronic device use and these symptoms.
3. The degree of slumped spinal posture during electronic device use was correlated with the severity and frequency of self-reported musculoskeletal symptoms.
4. Vergence facility and accommodative facility were correlated with the severity and frequency of self-reported eye symptoms and the Ocular Surface Disease Index, respectively.
5. Frequent breaks, physical activity, and focused-group programmes help reduce the negative impacts associated with excessive or problematic use of electronic devices.

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Introduction

Electronic devices have become indispensable among adolescents. In Hong Kong, 56% of adolescents own a smartphone, whereas >50% of primary school students and 90% of secondary school students own a smartphone or tablet. Adverse effects related to prolonged use or addiction to electronic devices include disruptions in mood, sleep quality, and academic performance, as well as various musculoskeletal pains. Associations have been reported between increased use of electronic devices and the presence of neck pain and low back pain in adolescents.[1]

The American Academy of Pediatrics recommends restricting children's media time to a maximum of 2 hours per day. Prolonged use of hand-held smart devices and computers can lead to computer vision syndrome, which encompasses a range of visual strain disorders, including burning, irritation, ocular dryness and tearing, eye fatigue, asthenopia, blurred vision, and slow focusing. These symptoms are related to fatigue of the visual system (eg, binocularity, accommodation, vergence, and oculomotility).[2] In Hong Kong, >50% of primary school students report symptoms of unclear vision and eye strain related to the use of portable electronic devices.[3]

Various types of parental controls to restrict or monitor children's internet access on smart devices have failed to solve this problem, given that 20% of adolescents aged 12 to 15 years know how to disable filters set up by their parents.[3] More proactive approaches that emphasise mutual and peer support for offline social lives and connections among teenagers and encourage physical and outdoor activity are recommended by governments and youth health organisations. Motivational factors involved in problematic internet use and excessive gaming are related to achievement, social engagement, and immersion. Internet use and gaming provide relief from dissatisfaction with life issues; therefore, a combination of child- and parent-focused interventions is required to address both personal and environmental factors associated with problematic use. Motivational interviewing is a person-centred counselling approach that helps enhance motivation for substantive behavioural change in alcohol and substance use, as well as motivation for self-management of diet and diabetes.[4] By incorporating a collaborative conversational style, motivational interviewing assists individuals in resolving ambivalence and increasing motivation and commitment to positive behavioural change related to the excessive use of electronic devices.

This study aimed to enhance adolescents' knowledge and awareness of the health risks associated with prolonged use of smart devices, and to promote healthy smart device use among primary and secondary school students.

Methods

Primary 5 to Secondary 4 adolescents from three schools in Hong Kong were invited to participate in a health survey, vision and spine assessments, and educational seminars. The physiotherapy team evaluated spinal posture during natural sitting and device use (using a two-dimensional spinal mapping method), proprioceptive sense of the spine (using a repositioning test), and spinal muscle strength and endurance. The optometry team conducted vision screening for accommodative amplitude and facility and vergence facility and assessed dry eye status using the Ocular Surface Disease Index (OSDI) and the phenol red test.

Students with higher scores were invited to participate in a group motivational interviewing programme conducted by a social worker. The programme enabled students to explore and formulate strategies and plans to promote healthier habits of electronic device use. The effectiveness of this programme was assessed using the Contemplation Ladder, the Readiness to Change Questionnaire, and the Internet Gaming Disorder Scale–Short Form.

Teachers and parents were invited to participate in health seminars to learn skills and strategies to facilitate behavioural modification related to adolescents' device use. Educational materials were designed to support the sustainability of in-house health education and the promotion of appropriate electronic device use.

Results

Of 1058 students participated, 61% and 78% spent >2 hours per day using electronic devices on school days and weekends/holidays, respectively; in particular, 18% and 36% spent ≥4 hours per day, respectively. Extended electronic device use was associated with increased prevalence and severity of musculoskeletal symptoms (ρ=0.28-0.33, P<0.001), visual symptoms (ρ=0.33-0.35, P<0.001), and poorer device use–related psychosocial health (ρ=0.38-0.47, P<0.001) [Fig]. Secondary school students reported greater device use and more severe symptoms than primary school students.

Among 560 students who completed vision and spine assessments, their craniovertebral angle, thoracic kyphosis angle, lumbar lordosis angle in natural sitting posture and smartphone use posture, proprioceptive accuracy, and cervical extensor strength and endurance were compared with their self-reported Musculoskeletal Discomfort Index, average time spent on electronic devices on weekdays, and school year (Table 1). Students who reported symptoms in the neck, back, or upper limb (ie, Musculoskeletal Discomfort Index >0) had a significantly greater forward head position in both natural sitting and smartphone use postures (P<0.001) and a more slumped sitting posture during smartphone use (P=0.001). Students in secondary school demonstrated more inadequate sitting postures (greater forward head position and

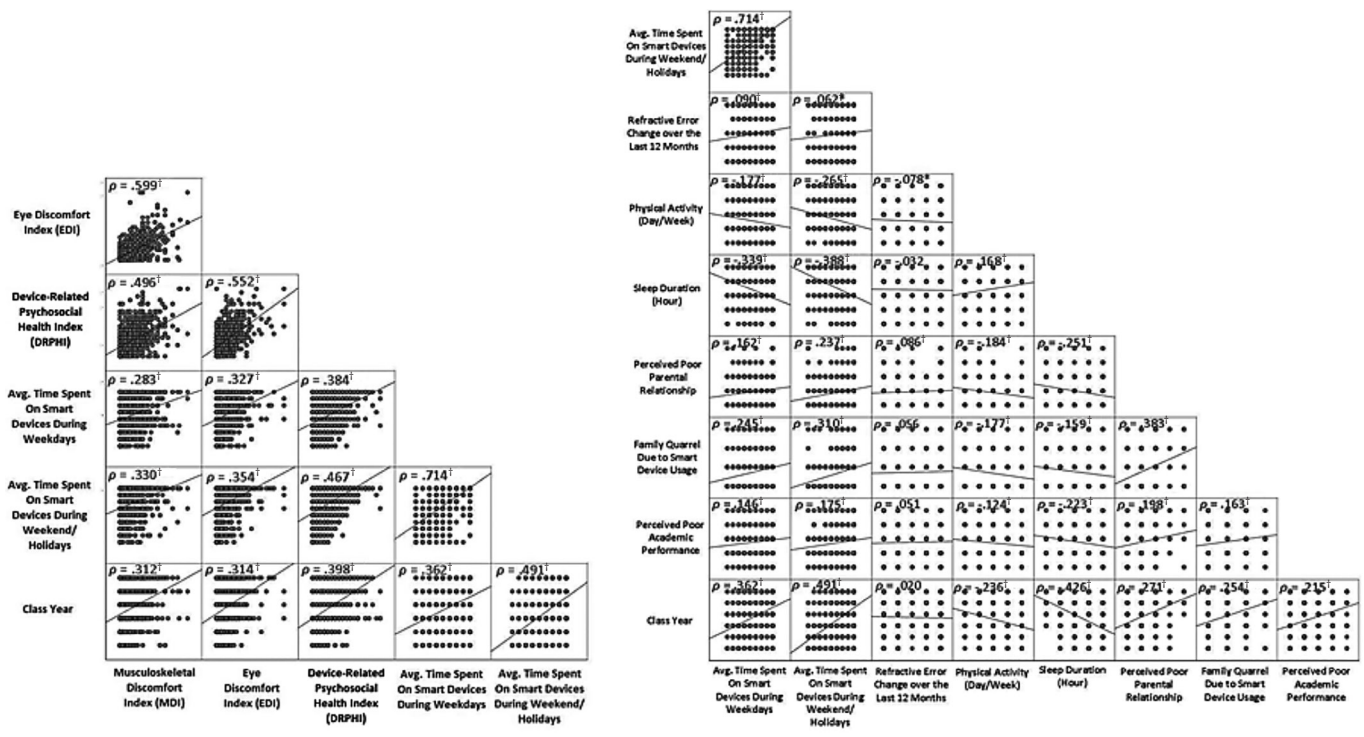

FIG. Spearman's rank correlations between device use and the Eye Discomfort Index, Musculoskeletal Discomfort Index, or Device-Related Psychosocial Health Index, and between device use and quality-of-life domains.

* P<0.05

† P<0.01

more slumped posture) than those in primary school (P<0.05).

Similarly, OSDI and vision results were compared with self-reported eye discomfort, average time spent on electronic devices on weekdays, and school year (Table 2). Vergence facility performance was significantly poorer among primary school students who used electronic devices for ≥2 hours per day, compared with those who used such devices for <2 hours. However, the opposite was observed among secondary school students. Among primary school students, both accommodative facility and vergence facility were poorer in the symptomatic group (Eye Discomfort Index >0 or OSDI >13), compared with the asymptomatic group.

Among 55 students with higher scores, the number of students in the Action stage of the Stage of Readiness to Change significantly increased after the group motivational interviewing programme and at the 3-month follow-up (Table 3). Tables 4 and 5 show the results of goal setting and the barriers to change identified by participants.

TABLE 1. Craniovertebral angle, thoracic kyphosis angle, and lumbar lordosis angle in natural sitting posture and smartphone use posture among students.

Posture	Musculoskeletal Discomfort Index		P value
	Asymptomatic (n=108)	Symptomatic (n=452)	
Natural sitting posture			
Craniovertebral angle, degrees	71.6±10.4	67.5±12.0	<0.001
Thoracic kyphosis angle, degrees	29.8±10.7	28.6±11.4	0.302
Lumbar lordosis angle, degrees	-8.4±12.9	-8.6±12.6	0.870
Smartphone use posture			
Craniovertebral angle, degrees	57.9±20.2	48.5±22.8	<0.001
Thoracic kyphosis angle, degrees	36.4±12.5	35.2±12.2	0.367
Lumbar lordosis angle, degrees	-5.3±15.2	0.1±15.6	0.001
	Average time spent on electronic devices on weekdays		
	<2 hours/day (n=158)	≥2 hours/day (n=402)	
Natural sitting posture			
Craniovertebral angle, degrees	69.1±11.8	68.0±11.8	0.295
Thoracic kyphosis angle, degrees	29.5±11.4	28.6±11.2	0.355
Lumbar lordosis angle, degrees	-9.3±13.3	-8.3±12.4	0.365
Smartphone use posture			
Craniovertebral angle, degrees	53.2±21.8	49.2±22.9	0.053
Thoracic kyphosis angle, degrees	35.9±11.4	35.3±12.6	0.636
Lumbar lordosis angle, degrees	-3.3±16.7	-0.1±15.2	0.029
	School year		
	Primary school (n=174)	Secondary school (n=386)	
Natural sitting posture			
Craniovertebral angle, degrees	77.7±4.9	64.1±11.6	<0.001
Thoracic kyphosis angle, degrees	27.1±9.8	29.6±11.8	0.012
Lumbar lordosis angle, degrees	-7.8±13.7	-9.0±12.1	0.300
Smartphone use posture			
Craniovertebral angle, degrees	70.6±8.3	41.2±21.1	<0.001
Thoracic kyphosis angle, degrees	33.2±11.7	36.5±12.4	0.003
Lumbar lordosis angle, degrees	-1.2±16.4	-0.9±15.3	0.844

Discussion

It is alarming that 18% and 36% of participants spent ≥4 hours per day using electronic devices on school days and weekends/holidays, respectively, which is more than twice the time limit suggested by the American Academy of Pediatrics. Secondary school students reported greater use of electronic devices than primary school students, highlighting the importance of early intervention to minimise development of unhealthy electronic device habits in youth.

The highest prevalence of musculoskeletal symptoms was reported in the neck region. There is a 4% to 7% increase in the odds ratio for musculoskeletal symptom development per additional hour of daily smartphone use.[5,6] Sustained cervical muscle contraction, flexed neck posture due to lower display placement, lack of postural breaks, and poor ergonomic workstation setup are potential mechanisms. Frequent breaks between classes or after-school activities to vary posture, or spending more time to physical education, should be proactively incorporated to help alleviate these physical impacts. Such additional interval breaks or physical education classes can reduce the risk of physical symptoms without sacrificing academic performance.[7]

Greater electronic device use was significantly associated with visual symptoms. One possible cause of the development and persistence of these symptoms is a decreased blink rate and an increased number of incomplete blinks during device use. Low blink rates increase corneal exposure to air, causing tear evaporation, dry eyes, and ocular irritation. Visual symptom severity was associated with school year, highlighting the need to develop and implement more effective strategies within school routines (eg, the 20-20-20 eye-resting rule and addition of 2 hours per day of outdoor activities), particularly given the potential long-term negative consequences of eye problems that develop during childhood.[8]

Prolonged device use was negatively associated with relationships with parents, highlighting the need for parental education and training to help parents effectively support their children in limiting device use while maintaining positive interactions. Parents may also help by providing more guidance on their children's device use and serving as positive role models.

Exposure to video games before sleep and viewing bright screens while engaging in tasks linked to emotional responses may increase an adolescent's

TABLE 2. Accommodative amplitude and facility and vergence facility among students.

School	Eye Discomfort Index		P value
	Asymptomatic (n=122)	Symptomatic (n=438)	
Primary school			
Accommodative amplitude, D	15.3±2.2	14.8±2.5	0.205
Accommodative facility, cpm	6.7±4.5	5.8±3.3	0.192
Vergence facility, cpm	9.8±5.2	8.0±4.7	0.026
Secondary school			
Accommodative amplitude, D	14.3±2.6	13.9±2.7	0.231
Accommodative facility, cpm	8.6±4.5	9.4±4.6	0.165
Vergence facility, cpm	14.0±5.5	14.4±6.1	0.640
	Average time spent on electronic devices on weekdays		
	<2 hours/day (n=158)	≥2 hours/day (n=402)	
Primary school			
Accommodative amplitude, D	15.1±2.7	14.8±2.4	0.512
Accommodative facility, cpm	6.5±3.4	5.9±3.8	0.336
Vergence facility, cpm	9.8±4.8	8.0±4.8	0.039
Secondary school			
Accommodative amplitude, D	13.9±2.7	14.0±2.7	0.796
Accommodative facility, cpm	8.9±4.7	9.4±4.5	0.362
Vergence facility, cpm	12.8±6.0	15.0±5.9	0.002
	Ocular Surface Disease Index		
	Asymptomatic (n=120)	Symptomatic (n=440)	
Primary school			
Accommodative amplitude, D	15.1±2.4	14.8±2.5	0.482
Accommodative facility, cpm	6.7±3.5	5.5±3.7	0.035
Vergence facility, cpm	8.6±4.9	8.3±4.8	0.793
Secondary school			
Accommodative amplitude, D	14.1±2.9	13.8±2.6	0.258
Accommodative facility, cpm	9.2±4.5	9.4±4.6	0.703
Vergence facility, cpm	14.3±5.9	14.4±6.1	0.891

Abbreviations: cpm = cycles per minute, D = diopters

TABLE 3. Motivational interviewing programme for intensive users.

Tool	Pre-treatment (n=55)*	Post-treatment (n=46)*	3 months (n=45)*
Internet Gaming Disorder Scale–Short Form	20.95±5.65	20.93±6.67	20.58±5.73
Stage of Readiness to Change			
Pre-contemplation	8	5	6
Contemplation	31	17	19
Action	16	24†	20†
Contemplation Ladder (0-10)	5.29±1.93	6.68±1.71	6.43±1.91

* Data are presented as mean±standard deviation or No. of participants.
† P<0.05

psychophysiological arousal, interfering with sleep. Insufficient sleep—detrimental to growth—is associated with fatigue and poor academic performance. These findings highlight the need to educate parents about effective strategies to limit the negative effects of device use on their children's sleep quality.

Students with musculoskeletal symptoms often exhibited a more forward head posture. A more kyphotic thoracic spine posture was consistently adopted by secondary school students while sitting and using smartphones. Compared with primary school students, secondary school students demonstrated at least a two-fold increase in the extent of forward head posture and greater thoracic kyphosis during smartphone use. Students with musculoskeletal symptoms or those in higher school years exhibited a more flexed posture, particularly in the cervical region, even when sitting naturally. This may be attributed to undesirable postural habits developed over time, especially prolonged slouched sitting. Early intervention to reinforce the importance of appropriate device use for preventive care is necessary. Regular breaks and exercises should be incorporated into daily routines to minimise the impact of electronic device use.

In the change plans, the most frequently mentioned goal was self-management (n=34, 44.7%), followed by academic study (n=20, 26.3%) and participation in other activities (n=13, 17.1%). Participants demonstrated awareness of their gaming or internet addiction or excessive screen time. Frustration with study and academic results may be linked to the development of gaming addiction.

The most frequently mentioned barriers to change included the use of gadgets and gaming devices (n=15, 29.4%), motivation for change (n=10, 19.6%), lack of self-management (n=7, 13.7%), and academic study (n=7, 13.7%). These findings are largely consistent with the reported change goals. Academic study functioned as both a goal and a barrier. Participants also reported the influence of physical condition (eg, tiredness and sleepiness), emotions, and social pressure from others (eg, playing with friends or siblings); however, these factors were reported less frequently and were therefore unlikely to be key barriers to change.

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Disclosure

The results of this research have been previously published in:

TABLE 4. Goals set by participants during the motivational interviewing programme.

Goals	Examples	No. (%) of goals set
Self-management	Improve self-control, reduce time spent on smartphones, sleep more, reduce gaming, reduce harm to eyes, stop procrastination	34 (44.7)
Academic	Academic study	20 (26.3)
Participation in other activities	More physical activity, more reading, engaging in more productive and fulfilling activities, more extracurricular activities, developing different hobbies	13 (17.1)
Broad goals related to future and development	Wealth, broadening horizons, character development, lifestyle, understanding the world	5 (6.6)
Specific personal goals	Relationships with parents or friends, weight reduction, diet	4 (5.3)

TABLE 5. Barriers to change identified by participants during the motivational interviewing programme.

Barriers	Examples	No. (%) of barriers to change
Use of gadgets and gaming devices	Attraction of new games or videos, gaming, smartphones, electronic devices	15 (29.4)
Motivation	Laziness, lack of motivation, easy to give up	10 (19.6)
Self-management	Poor time management, lack of self-control, number of choices, urgency of other matters	7 (13.7)
Study	Academic burden, study or work	7 (13.7)
Body condition	Sleepiness, tiredness, sickness	4 (7.8)
Pressure from others	Chatting with friends, peer pressure, disagreement with parents	3 (5.9)
Emotions	Boredom, feeling discouraged	2 (3.9)

1. Tsang SMH, Cheing GLY, Chan JWK. Severity of slouched posture during smartphone use is associated with the musculoskeletal discomfort, daily usage, and school year among adolescents. Ergonomics 2023;66:1340-53.
2. Tsang SMH, Cheing GLY, Lam AKC, et al. Excessive use of electronic devices among children and adolescents is associated with musculoskeletal symptoms, visual symptoms, psychosocial health, and quality of life: a cross-sectional study. Front Public Health 2023;11:1178769.
3. Tse N, Siu A, Tsang S, Jensen MP. Group motivational interviewing for adolescents at risk of internet gaming disorder: a mixed-methods preliminary evaluation. Clin Soc Work J 2026;54:44-55.

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References

1. Silva GR, Pitangui AC, Xavier MK, Correia-Junior MA, De Araujo RC. Prevalence of musculoskeletal pain in adolescents and association with computer and videogame use. J Pediatr (Rio J) 2015;92:188-96.
2. Blehm C, Vishnu S, Khattak A, Mitra S, Yee RW. Computer vision syndrome: a review. Surv Ophthalmol 2005;50:253-62.
3. Report of Advisory Group on Health Effects of Use of Internet and Electronic Screen Products. Accessed 15 December 2025. Available from: https://www.studenthealth.gov.hk/english/internet/report/files/e_report_wa.pdf
4. Miller WR, Rollnick S. Motivational Interviewing: Helping People Change and Grow. 3rd ed. Guidford Press; 2012.
5. Shan Z, Deng G, Li J, Li Y, Zhang Y, Zhao Q. Correlational analysis of neck/shoulder pain and low back pain with the use of digital products, physical activity and psychological status among adolescents in Shanghai. PLoS One 2013;8:e78109.
6. Vitta A, Bento TPF, Cornelio GP, Perrucini PDO, Felippe LA, Conti MHS. Incidence and factors associated with low back pain in adolescents: a prospective study. Braz J Phys Ther 2021;25:864-73.
7. Waongenngarm P, Areerak K, Janwantanakul P. The effects of breaks on low back pain, discomfort, and work productivity in office workers: a systematic review of randomized and non-randomized controlled trials. Appl Ergon 2018;68:230-9.
8. Alabdulkader B. Effect of digital device use during COVID-19 on digital eye strain. Clin Exp Optom 2021;104:698-704.

Combination of mind-body physical exercise, cognitive training, and nurse-led risk factor modification for older adults with mild cognitive impairment: a randomised controlled trial (abridged secondary publication)

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KEY MESSAGES

1. We compared the effects of health advice alone, nurse-led risk factor modification (RFM) alone, and a combination of cognitive training, mind-body physical exercise, and nurse-led RFM on preventing cognitive decline in older adults with mild cognitive impairment (MCI).
2. Although Alzheimer's Disease Assessment Scale–Cognitive Subscale scores significantly improved from baseline across all three groups, the combination and nurse-led RFM groups did not demonstrate additional benefits relative to the health advice group.
3. Future research should focus on identifying the characteristics of older adults with MCI who derive the most benefit from interventions, and on more accurately describing the natural history of MCI.
4. Future studies can also explore optimal intervention dosage, including the intensity, duration, and formats of physical exercise and cognitive training.
5. Early identification of MCI and improved strategies for participant retention, with more intensive follow-up, may be needed.

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Introduction

Dementia and cognitive impairments are major public health challenges. According to the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), in older adults at risk of dementia, interventions combining exercise, cognitive training, dietary changes, and vascular risk monitoring can significantly enhance cognitive function, compared with regular health advice.[1] Nurse-led care can achieve health outcomes comparable to those of doctor-led care. However, there is a lack of randomised controlled trials evaluating the effectiveness of nurse-led risk factor modification (RFM) or its combination with physical exercise and cognitive training on cognitive function in older adults.[2] This study aimed to compare the effects of health advice alone, nurse-led RFM alone, and a combination of cognitive training, mind-body physical exercise, and nurse-led RFM on preventing cognitive decline in older adults with mild cognitive impairment (MCI).

Methods

Older adults aged 60 to 80 years with MCI (based on a score of 19 to 25, adjusted for education, on the Hong Kong version of the Montreal Cognitive Assessment[3] [HK-MoCA]) and without any life-threatening diseases were recruited from various primary care and community settings. Individuals with a diagnosis of dementia, participation in a concurrent lifestyle modification programme, a history of bipolar disorder or psychosis, or communication difficulties were excluded. Psychotropic medications were required to remain stable for at least 3 months prior to the baseline assessment and throughout the study. Participants were randomly assigned to receive health advice alone, nurse-led RFM alone, or a combination of cognitive training, mind-body physical exercise, and nurse-led RFM for 15 months.

Health advice was delivered through pamphlets emphasising healthy diets and promoting physical, cognitive, and social activities aimed at managing risk factors, preventing cognitive decline, and reducing disability.

Nurse-led RFM was based on the FINGER trial protocol.[1] A nurse with >20 years of experience offered personalised lifestyle modifications on a quarterly basis. A physician also reviewed blood test results, physical examination findings, and cardiovascular

and metabolic health. Key risk factors considered included poor control of blood pressure, glucose, and lipid levels, as well as body mass index >25 kg/m^2, smoking, physical inactivity, and unhealthy diet. Dietary goals included increasing fruit and vegetable intake, choosing low-fat meat products, limiting sucrose to 50 g/day, and consuming two or more servings of fish weekly. Motivational interviewing techniques were used to promote behavioural change. Cardiovascular risk was assessed using the QRISK3 score, with the goal of maintaining 10-year cardiovascular risk <10%.

The combination of mind-body physical exercise, cognitive training, and nurse-led RFM included practising the 24-form simplified Tai Chi for 30 minutes three times per week, led by a trained Tai Chi master or physical therapist. Participants were encouraged to continue practising using audio or video recordings afterwards. Additionally, three 1-hour group cognitive sessions per week were provided, involving leisure activities that required substantial cognitive engagement.

Assessments were conducted at baseline and at 6, 12, and 15 months. At baseline, participants met with primary care clinicians for a health examination and medical history review. The nurse provided both verbal and written guidance on physical and cognitive activities, as well as dietary recommendations to enhance vascular health and mitigate risks. Outcome measures included the Chinese version of the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog), the Clinical Dementia Rating Scale–Sum of Boxes, the Disability Assessment for Dementia, the European Quality of Life Questionnaire, five-level version and its visual analogue scale, the Geriatric Depression Scale, the Geriatric Anxiety Scale, a dietary adherence score derived from a shortened Food Frequency Questionnaire, the Physical Activity Scale for the Elderly, the Alcohol Use Disorders Identification Test–Concise, and health service utilisation.

A linear mixed model was used to assess changes and between-group differences in outcomes across the three groups over time. Outcome scores were the dependent variables, whereas the intervention group, time, and their interaction served as predictors. The intention-to-treat principle was followed.

Results

In total, 129 male and 327 female participants (mean age, 70.1 years) were equally randomised into one of the three groups. The groups were comparable at baseline (Table 1). Attendance rates for the nurse-led RFM sessions were 88.8% in the combination group and 92.5% in the RFM group. Within the combination group, 55.1% of participants attended the exercise sessions, whereas 54.6% attended the cognitive sessions.

ADAS-Cog scores significantly improved across all three groups at 6, 12, and 15 months ($P<0.05$). Estimated between-group treatment effects revealed no significant differences in ADAS-Cog scores or any secondary outcomes among groups at any follow-up time (Table 2).

Compared with those who completed all assessments, participants who missed any follow-up assessment had worse baseline ADAS-Cog scores (11.9±4.9 vs 10.4±4.1, P=0.006) and HK-MoCA scores (22.2±2.1 vs 22.7±1.9, P=0.048).

Discussion

Significant ADAS-Cog improvements were observed across all three groups at each follow-up. Even the minimal health advice intervention led to cognitive improvements in many participants with MCI. These improvements may be attributable to the natural course of MCI, regression to the mean, and practice effects. Epidemiological study results suggest that approximately 45% of patients remain stable, whereas up to 44% revert to normal cognition within 1 year.[4,5] Regression to the mean, in which extreme cognitive scores tend to normalise over time, suggests that the ADAS-Cog improvements could reflect natural fluctuations rather than genuine cognitive enhancement. Additionally, practice effects may have contributed to improvements observed in the health advice group; participants might also have benefited from unrecorded interventions, given that they were already active older adults within community and primary care settings.

The RFM group showed a non-significant trend towards better ADAS-Cog outcomes, compared with the health advice group. According to a scoping review, none of four nurse-led interventions targeting cognitive outcomes in dementia or MCI demonstrated significant positive effects. Most studies excluded patients with MCI or those at an early stage of dementia. Participants at lower risk may be less likely to benefit from interventions, suggesting that not all individuals with MCI require immediate intervention. Therefore, future research should prioritise early identification of high-risk MCI patients and more intensive follow-ups in this population.

There were no additional benefits in cognitive function or any secondary outcomes in the combination group, compared with the RFM and health advice groups. The attendance rates for physical exercise and cognitive training sessions exceeded 50% and were comparable to the 60% for physical activity and 47.2% for cognitive training noted in the FINGER study.[1] Future research should focus on identifying the optimal frequency and intensity of interventions that are both acceptable and effective for individuals with MCI.

TABLE 1. Characteristics of participants at baseline.

Characteristic	Total (n=456)*	Combination (n=152)*	Risk factor modification (n=152)*	Health advice (n=152)*	P value
Age, y	70.1±4.9	70.9±4.8	69.8±5.0	69.6±4.8	0.061
Male	129 (28.3)	49 (32.2)	39 (25.7)	41 (27.0)	0.403
Married	285 (62.5)	95 (62.5)	92 (60.5)	98 (64.5)	0.777
Education >6 y	243 (53.3)	80 (52.6)	79 (52.0)	84 (55.3)	0.831
No. of people living together	1.6±1.4	1.5±1.2	1.8±1.5	1.5±1.2	0.084
Living alone	92 (20.2)	30 (19.7)	36 (23.7)	26 (17.1)	0.355
No. of children					0.914
0	37 (8.1)	11 (7.2)	13 (8.6)	13 (8.6)	
1	84 (18.4)	25 (16.4)	30 (19.7)	29 (19.1)	
≥2	335 (73.5)	116 (76.3)	109 (71.7)	110 (72.4)	
Employed	32 (7.0)	9 (5.9)	11 (7.2)	12 (7.9)	0.790
Family monthly income ≥HK$4000	237 (52.0)	78 (51.3)	89 (58.6)	70 (46.1)	0.078
Recipient of Comprehensive Social Security Assistance†	20 (4.4)	10 (6.6)	2 (1.3)	8 (5.3)	0.066
Medical comorbidities					0.338
0-1	106 (23.2)	31 (20.4)	39 (25.7)	36 (23.7)	
2-3	157 (34.4)	62 (40.8)	45 (29.6)	50 (32.9)	
≥4	193 (42.3)	59 (38.8)	68 (44.7)	66 (43.4)	
Ever smoker	69 (15.1)	23 (15.1)	24 (15.8)	22 (14.5)	0.950
Hong Kong version of Montreal Cognitive Assessment	22.6±2.0	22.6±1.9	22.8±1.9	22.4±2.1	0.276
Alzheimer's Disease Assessment Scale–Cognitive Subscale	10.7±4.3	10.2±3.9	10.9±4.7	11.0±4.3	0.241
Clinical Dementia Rating Scale–Sum of Boxes	1.6±0.9	1.5±0.8	1.6±1.0	1.6±0.8	0.698
Disability Assessment for Dementia	98.0±3.4	98.1±3.1	97.9±3.6	98.1±3.4	0.795
European Quality of Life Questionnaire (five-level version)	0.86±0.15	0.86±0.14	0.86±0.15	0.87±0.14	0.790
European Quality of Life Questionnaire (visual analogue scale)	69.5±14.1	70.5±13.4	69.3±14.6	68.8±14.3	0.558
Geriatric Depression Scale	4.2±3.5	3.8±3.2	4.3±3.7	4.5±3.6	0.231
Geriatric Anxiety Scale	4.6±5.6	4.2±5.4	4.5±5.4	5.1±5.9	0.369
Physical Activity Scale for the Elderly	91.1±40.6	92.2±40.9	91.6±36.8	89.6±44.0	0.844
Dietary adherence score	7.0±1.3	7.1±1.3	6.9±1.3	7.0±1.4	0.407
Alcohol Use Disorders Identification Test–Concise	0.8±1.5	0.8±1.4	0.8±1.6	0.8±1.4	0.926
No. of health service utilisations	6.3±6.4	6.4±6.9	6.3±6.4	6.3±5.9	0.975

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

This study had several limitations. First, no assessment was conducted at 3 months after the initial 3-month intervention; the cognitive training and exercise programmes lasted only 3 months. Due to resource constraints, only a 6-month follow-up was performed. Second, a substantial proportion of participants improved with the minimal health advice intervention alone, making it difficult to detect between-group differences. The broad MCI criteria (an HK-MoCA score of 19 to 25) may have included participants with milder cognitive impairment who improved naturally without intervention. Third, the compliance rates for exercise and cognitive training were only 50%; these likely were affected by the COVID-19 pandemic, which may have influenced outcomes in the intervention group.

TABLE 2. Estimated treatment effects between groups at 6-, 12-, and 15-month follow-ups.

Outcome	Treatment effect (95% confidence interval)		
	Combination vs health advice	Risk factor modification vs health advice	Combination vs risk factor modification
Alzheimer's Disease Assessment Scale–Cognitive Subscale			
6 months	-0.2 (-1.3 to 0.8)	-0.8 (-1.9 to 0.2)	0.6 (-0.4 to 1.6)
12 months	0.1 (-1.1 to 1.4)	-0.9 (-2.2 to 0.3)	1.1 (-0.2 to 2.3)
15 months	0.3 (-1.0 to 1.7)	-0.6 (-1.9 to 0.8)	0.9 (-0.4 to 2.2)
Clinical Dementia Rating Scale–Sum of Boxes			
6 months	-0.1 (-0.3 to 0.1)	-0.1 (-0.3 to 0.1)	0.0 (-0.2 to 0.2)
12 months	0.0 (-0.2 to 0.2)	0.1 (-0.2 to 0.3)	-0.1 (-0.3 to 0.2)
15 months	-0.1 (-0.3 to 0.1)	-0.1 (-0.4 to 0.1)	0.0 (-0.2 to 0.3)
Disability Assessment for Dementia			
6 months	0.6 (-0.2 to 1.4)	0.8 (-0.1 to 1.6)	-0.1 (-1.0 to 0.7)
12 months	0.3 (-0.6 to 1.2)	0.2 (-0.8 to 1.1)	0.1 (-0.8 to 1.0)
15 months	0.1 (-0.8 to 1.1)	0.2 (-0.7 to 1.2)	-0.1 (-1.0 to 0.8)
European Quality of Life Questionnaire (five-level version)			
6 months	0.03 (-0.01 to 0.06)	0.03 (-0.01 to 0.06)	0.00 (-0.03 to 0.04)
12 months	0.01 (-0.03 to 0.05)	0.01 (-0.03 to 0.05)	0.00 (-0.04 to 0.04)
15 months	0.04 (-0.01 to 0.09)	0.02 (-0.03 to 0.07)	0.02 (-0.02 to 0.07)
European Quality of Life Questionnaire (visual analogue scale)			
6 months	-0.2 (-3.3 to 2.9)	0.9 (-2.3 to 4.2)	-1.1 (-4.2 to 2.0)
12 months	0.6 (-3.3 to 4.5)	-0.2 (-4.2 to 3.8)	0.8 (-3.0 to 4.7)
15 months	-0.3 (-4.6 to 3.9)	-0.3 (-4.7 to 4.0)	0.0 (-4.2 to 4.2)
Geriatric Depression Scale			
6 months	0.1 (-0.6 to 0.8)	-0.2 (-1.0 to 0.5)	0.3 (-0.4 to 1.1)
12 months	-0.1 (-1.0 to 0.8)	-0.3 (-1.2 to 0.6)	0.2 (-0.7 to 1.1)
15 months	0.6 (-0.4 to 1.6)	-0.4 (-1.4 to 0.6)	1.0 (0.0 to 1.9)
Geriatric Anxiety Scale			
6 months	0.5 (-0.7 to 1.7)	0.0 (-1.1 to 1.2)	0.5 (-0.7 to 1.6)
12 months	0.6 (-0.9 to 2.1)	0.6 (-0.8 to 2.1)	0.0 (-1.5 to 1.4)
15 months	1.3 (-0.4 to 2.9)	-0.3 (-1.9 to 1.3)	1.5 (0.0 to 3.1)
Physical Activity Scale for the Elderly			
6 months	-3.5 (-12.9 to 5.9)	-3.1 (-12.3 to 6.1)	-0.1 (-9.5 to 9.2)
12 months	1.3 (-10.5 to 13.0)	-5.1 (-16.5 to 6.2)	6.7 (-4.6 to 18.0)
15 months	-1.0 (-13.8 to 11.8)	-9.1 (-21.4 to 3.3)	8.2 (-3.8 to 20.1)
Dietary adherence score			
6 months	0.3 (-0.1 to 0.6)	0.3 (0.0 to 0.7)	-0.1 (-0.4 to 0.3)
12 months	0.3 (-0.1 to 0.7)	0.3 (-0.1 to 0.7)	0.0 (-0.4 to 0.4)
15 months	0.3 (-0.1 to 0.7)	0.2 (-0.2 to 0.6)	0.1 (-0.3 to 0.5)
Alcohol Use Disorders Identification Test–Concise			
6 months	0.0 (-0.3 to 0.2)	0.1 (-0.2 to 0.3)	-0.1 (-0.4 to 0.1)
12 months	0.1 (-0.2 to 0.4)	0.0 (-0.4 to 0.3)	0.1 (-0.2 to 0.5)
15 months	0.1 (-0.2 to 0.5)	0.0 (-0.4 to 0.3)	0.1 (-0.2 to 0.5)
No. of health service utilisations			
6 months	-0.4 (-2.1 to 1.2)	0.4 (-1.4 to 2.2)	-0.9 (-2.8 to 1.1)
12 months	-0.3 (-2.3 to 1.7)	1.4 (-0.7 to 3.6)	-1.8 (-4.1 to 0.6)
15 months	0.3 (-1.8 to 2.4)	0.2 (-2.2 to 2.5)	0.2 (-2.3 to 2.6)

Conclusion

A combination of cognitive training, mind-body physical exercise, and nurse-led RFM did not provide additional benefits over health advice alone regarding cognitive function improvement among older adults with MCI. Future research should focus on identifying specific characteristics of older adults with MCI who are most likely to benefit from interventions and on more accurately describing the natural history of MCI. Additionally, it is essential to explore optimal dosages, including the intensity, duration, and formats of physical exercise and cognitive training, to improve cognitive function and ensure high compliance. Early identification of MCI and better retention strategies with more intensive follow-up may be needed.

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Disclosure

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1. Xu Z, Zhang D, Yip BH, et al. Combined mind-body physical exercise, cognitive training, and nurse-led risk factor modification to enhance cognition among older adults with mild cognitive impairment in primary care: a three-arm randomised controlled trial. Lancet Healthy Longev 2025;6:100706.

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References

1. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 2015;385:2255-63.
2. Lam LC, Chan WC, Leung T, Fung AW, Leung EM. Would older adults with mild cognitive impairment adhere to and benefit from a structured lifestyle activity intervention to enhance cognition?: a cluster randomized controlled trial. PLoS One 2015;10:e0118173.
3. Yeung PY, Wong LL, Chan CC, Leung JL, Yung CY. A validation study of the Hong Kong version of Montreal Cognitive Assessment (HK-MoCA) in Chinese older adults in Hong Kong. Hong Kong Med J 2014;20:504-10.
4. Hu C, Yu D, Sun X, Zhang M, Wang L, Qin H. The prevalence and progression of mild cognitive impairment among clinic and community populations: a systematic review and meta-analysis. Int Psychogeriatr 2017;29:1595-608.
5. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. Lancet 2006;367:1262-70.

Identification of pathogenic genomic variants in idiopathic azoospermia by long-fragment-read genome sequencing: abridged secondary publication

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KEY MESSAGES

1. We recruited 100 men with idiopathic infertility who had negative findings in karyotype analysis and Y-microdeletion testing for long-fragment-read genome sequencing (GS).
2. Long-fragment-read GS identified likely clinically significant variants in 32 men (19 with nonobstructive azoospermia and 13 with severe oligoasthenozoospermia); the diagnostic yield was 32.0%.
3. Genetic investigation of variants by long-fragment-read GS facilitates both understanding of infertility mechanisms and patient management, including sperm retrieval through testicular biopsy, intracytoplasmic sperm injection, and/or preimplantation genetic testing via in vitro fertilisation.
4. Long-fragment-read GS can be used as a second-tier approach for the genetic diagnosis of infertile men.

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Introduction

Male infertility affects approximately 7% of the male population.[1] Its phenotypic spectrum is heterogeneous, ranging from the absence of sperm to alterations in sperm quality.[1] Genetic testing is recommended by the American Society for Reproductive Medicine[2] for men with nonobstructive azoospermia (NOA) or severe oligoasthenozoospermia (OAT) to clarify the aetiology prior to surgical intervention,[3] including polymerase chain reaction (PCR) and karyotype analyses for Y-microdeletions and chromosomal abnormalities, respectively. Exome sequencing provides a diagnostic yield of approximately 20%.[4,5] We developed multiple-barcoded long-fragment-read genome sequencing (GS)[6] for comprehensive detection of copy-number variants (CNVs), structural variants (SVs), single-nucleotide variants (SNVs), small insertions/deletions (indels), and regions of absence of heterozygosity (AOH). We used this long-fragment-read GS to assess 100 men with idiopathic infertility and identified potential causative variants in 32 men, revealing a diagnostic yield of 32.0%.

Methods

We recruited men with severe OAT (<5 million sperm/mL ejaculate fluid and/or sperm malformation) or azoospermia with elevated follicle-stimulating hormone, or with negative results from Y-microdeletion and karyotype analyses.

Buffy coats were retrieved for long DNA extraction and subjected to long-fragment-read GS at >40-fold read depth.[6] RNA was extracted. SNVs/indels, CNVs, SVs, and regions with AOH were verified by Sanger sequencing, breakpoint-junction-specific PCR, and quantitative PCR. Ten cases with potential causative variants were also subjected to long-read sequencing. RNA sequencing with enrichment of messenger RNA was performed for >10 Gb data per sample. Paired-end reads were aligned to the human reference genome (hg19) with STAR. Expression patterns of candidate genes were compared with our in-house fertile controls. Two published single-cell sequencing datasets,[7,8] consisting of 74 845 cells derived from 12 time points in prenatal and postnatal testicular development, were curated by our Temporal Expression during Development Database[9] for cell type–specific expression analysis.

Results

In total, 63 men with NOA and 37 men with severe OAT were recruited (Table 1). Long-fragment-read GS identified likely clinically significant variants in 32 men (19 with NOA and 13 with severe OAT); the diagnostic yield was 32.0%. There were no significant differences in the diagnostic yields of each variant type between NOA and OAT groups (Table 2).

TABLE 1. Characteristics of 100 men with idiopathic infertility.

Characteristic	All (n=100)*	Nonobstructive azoospermia (n=63)*	Severe oligoasthenozoospermia (n=37)*	P value
Age, y	36±5	36±5.7	36±4.4	0.998
Follicle-stimulating hormone, IU/mL	20.7±13.2	24.9±13.1	11.1±6.0	<0.001
Testosterone, ng/dL	12.7±6.4	12.3±12.3	13.9±4.1	0.450

* Data are presented as mean ± standard deviation.

TABLE 2. Diagnostic yields of different causative variants in 100 men with idiopathic infertility.

Variant	All (n=100)*	Nonobstructive azoospermia (n=63)*	Severe oligoasthenozoospermia (n=37)*	P value
Single-nucleotide variants, small insertions/deletions	11	8	3	0.705
Copy-number variants, structural variants	16	9	7	0.743
Both	5	2	3	0.537

* Data are presented as No. of patients.

Long-fragment-read GS identified compound heterozygosity for pathogenic/likely pathogenic (P/LP) variants in seven men. Five of them involved one SNV and one CNV in an autosomal recessive disease-causing gene. For instance, in patient MI#33, we identified a heterozygous missense SNV (NM_015180:c.18389A>T:p.K6130I) and a heterozygous deletion (seq[GRCh37] del(14)(q23.2) NC_000014.8:g.64454090_64458143del) in the *SYNE2* gene (Fig 1). Both variants were predicted to result in loss of function. Given that *SYNE2* is part of a family of proteins involved in sperm-head formation[10] and shows significantly reduced expression in men with NOA,[11] biallelic loss of function might underlie its pathogenicity.

Among the 16 men with identified P/LP CNVs/SVs, five had these variants on the X chromosome. Patient MI#16 was diagnosed with NOA. Ultrasound examination revealed small testes (5 cc) and a small epididymal cyst. A hemizygous 1.14 Mb deletion in Xq28 was detected (seq[GRCh37] del(X)(q28) chrX:g.150838316_151978891del), involving the *MAGEA* and *CSAG* gene clusters, as well as the *FATE1* gene; however, none was expressed in the buffy coats (Fig 2). The *MAGEA* gene cluster is crucial for maintaining normal testicular size in mice, and knockout findings suggest that specific defects occur during the first wave of spermatogenesis. Single-cell sequencing data indicated *MAGEA* expression in primordial germ cells. The protein encoded by *FATE1* is known to regulate early testicular differentiation and cell proliferation, and *FATE1* is highly expressed in Sertoli cells during early testicular development. In comparison, depletion of *CSAG1* disrupts centrosomes and leads to multipolar spindles during mitosis, although no expression of CSAG1 was identified in fetal testicular samples. Both *FATE1* and *CSAG1* are highly expressed in adult germ cells. Therefore, the lack of expression of these genes likely contributed to small testes (*MAGEA* gene cluster and *FATE1*) and azoospermia (*CSAG1*).

P/LP CNVs/SVs involving autosomal chromosomes were identified in 11 men (five with NOA and six with OAT). Patient MI#48 had severe OAT. A 53-kb copy-number gain (seq[GRCh37] dup(2)(q31.1) chr2:g.171170285_171223517dup) involving the eighth exon (NM_001083615) of *MYO3B* on 2q31.1 was inserted into the fourth intron (NM_021951) of *DMRT1* (Fig 3). Flanking the insertion was a duplication (seq[GRCh37] dup(9)(p24.3) chr9:g.910281_931988dup) involving the fourth exon of *DMRT1*, which resulted in *DMRT1* truncation. *DMRT1* is highly expressed in prenatal Sertoli cells and primordial germ cells, in adulthood, in spermatogonia and early spermatids. Additionally, heterozygous deletion of *DMRT1* causes non-syndromic 46,XY disorders of sexual development.[12]

Long-fragment-read GS also detected multiple regions with AOH in four men with NOA. Two interstitial regions with AOH were identified, with an overall size of 18.7 Mb in patient MI#53, with suspected uniparental disomy of chromosome 6. However, there was an absence of causative SNVs/indels in genes related to male infertility. In comparison, the overall sizes of regions with AOH identified in patients MI#81, MI#77, and MI#73 were 68 Mb, 81.3 Mb, and 218.6 Mb, respectively, suggesting parental consanguinity. In patient MI#77, a 7.9-kb homozygous deletion involving the 5′ end

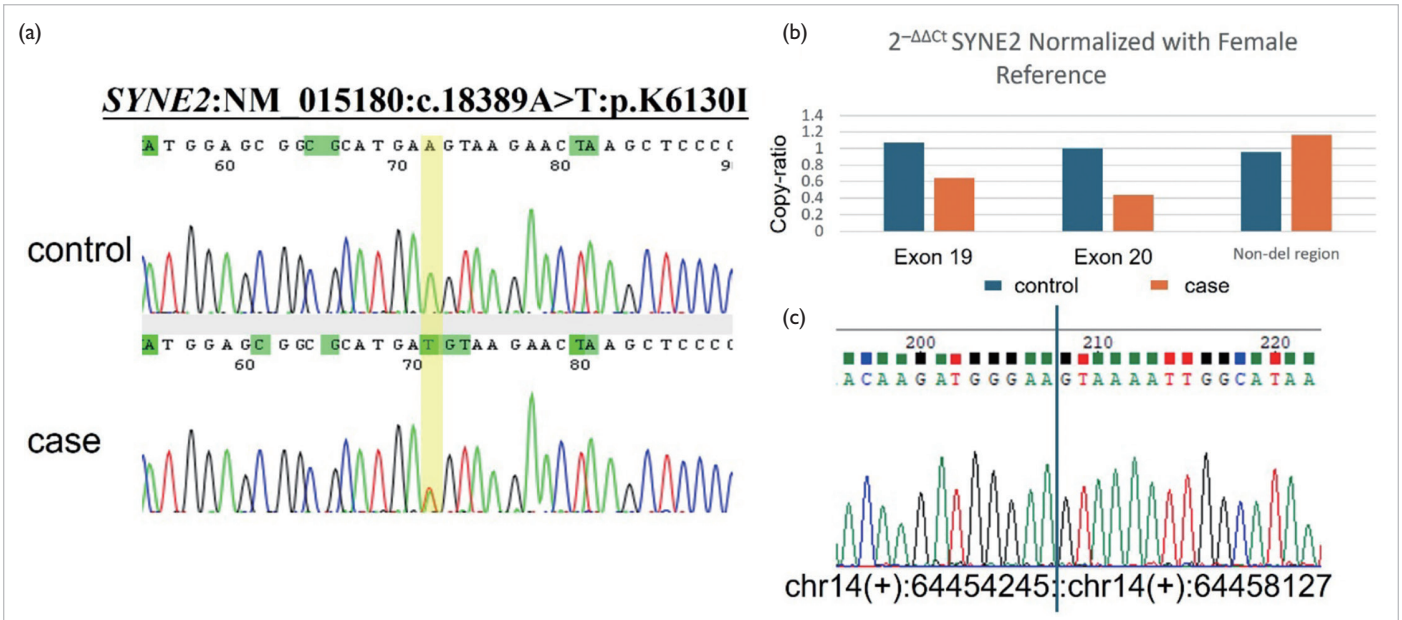

FIG 1. Compound heterozygosity of variants identified in patient MI#33: (a) Sanger sequencing confirmed the presence of the heterozygous variant. (b) Reverse transcription quantitative polymerase chain reaction confirmed a heterozygous deletion. (c) Breakpoint-specific polymerase chain reaction and Sanger sequencing revealed the junction sequence of this heterozygous deletion (3.8 kb in size).

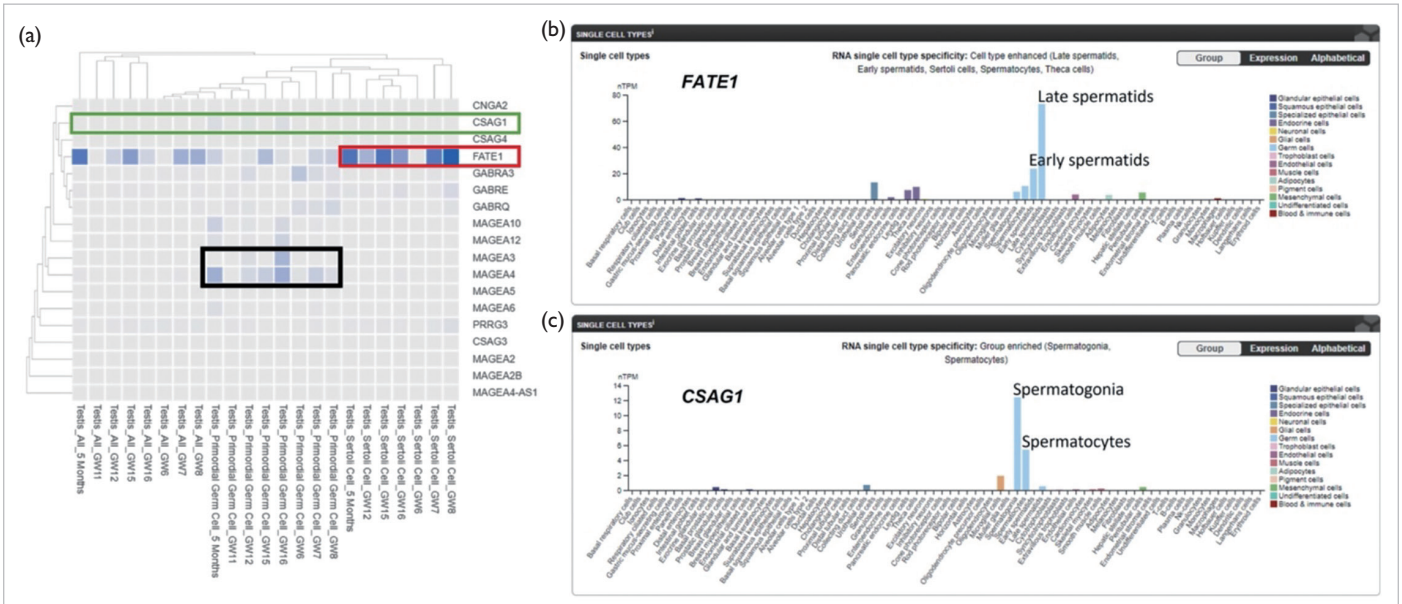

FIG 2. Gene expression involving the hemizygous deletion in patient MI#16: (a) Clustering of gene expression from single-cell sequencing during fetal testicular development: the top box shows the absence of expression in each identified cell type for *CSAG1*, the middle box shows the expression profiles of *FATE1* in Sertoli cells, and the bottom box displays the expression patterns of *MAGEA* gene cluster in primordial germ cells. (b) and (c) Expression profiles of *FATE1* and *CSAG1* in adult germ cells.

and first exon of the *NSUN7* gene was identified due to parental consanguinity.[13]

Discussion

Long-fragment-read GS identified clinically significant variants that potentially explain male infertility phenotypes in 32 of 100 men with idiopathic infertility. It was able to detect point mutations and smaller CNVs/SVs, compared with mate-pair sequencing.[14]

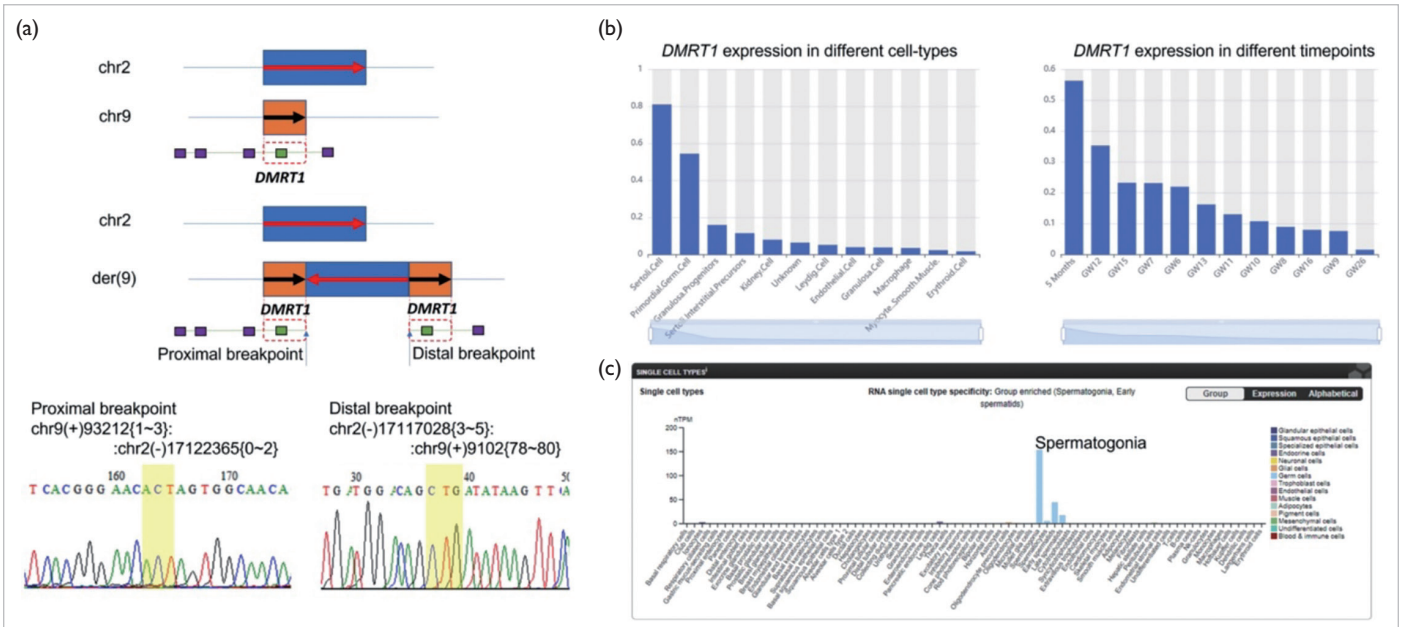

FIG 3. An interchromosomal insertion identified in patient MI#48: (a) The upper panel indicates the composition of normal chromosomes 2 and 9, whereas the lower panel indicates abnormalities at the 53.2 kb segment (chr2) and the 21.7 kb segment (chr9), respectively. Arrows indicate sequence orientation. Composition of der(9) shows insertion of a segment from 2q31.1 in antisense orientation, with subsequent duplication of a segment originating from 9p24.3. Breakpoint junction–specific polymerase chain reaction and Sanger sequencing show sequence microhomologies at both breakpoint junctions. (b) Abundance of *DMRT1* gene expression in different cell types and time points during testicular development. (c) Expression profile of *DMRT1* in adult germ cells.

Current management for patients with NOA is to perform testicular biopsy, followed by in vitro fertilisation through intracytoplasmic sperm injection (ICSI). Other factors may contribute to ICSI failure, even after sperm retrieval. Thus, information regarding the likelihood of ICSI failure is important for counselling. For severe OAT, knowledge of pathogenic variants is important to facilitate further genetic counselling if preimplantation testing is under consideration, along with conception by in vitro fertilisation and ICSI. Taken together, genetic investigation of variants using long-fragment-read GS is important for understanding the mechanisms of infertility and informing patient management.

Future research may make use of long-fragment-read GS, which achieved a diagnostic yield of 32.0%. Additionally, 21 cases were fully or partially attributed to CNVs/SVs, which could not be readily detected by exome sequencing or conventional GS. Annotation and interpretation of these intragenic changes are warranted because some might be causative in patients via dysregulation of disease-causing genes. Furthermore, establishment of the Temporal Expression during Development Database provides cell- or tissue-type- and time-point-specific expression profiles of target genes. Although RNA sequencing was conducted, the pathogenicity of genomic changes could not be confirmed by the presence of gene expression aberrations or splicing defects, given that most target genes showed no expression. Therefore, establishment of these profiles would enable better understanding of the contributions of genomic changes to infertility. Follow-up studies to investigate potential management options are warranted. Some genomic variants were correlated with clinical outcomes. Because certain variants are known to affect one or more testicular cell types, such as Leydig cells and Sertoli cells, future studies should explore potential applications of cell-type-specific treatment options or even gene therapy.

Conclusion

Long-fragment-read GS can be used as a second-tier approach for the genetic diagnosis of infertile men.

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Disclosure

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1. Zhou Z, Tan C, Chau MHK, et al. TEDD: a database of temporal gene expression patterns during multiple developmental periods in human and model organisms. Nucleic Acids Res 2023;51:D1168-78.
2. Dong Z, Qian J, Law TSM, et al. Mate-pair genome sequencing reveals structural variants for idiopathic male infertility. Hum Genet 2023;142:363-77.

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References

1. Krausz C, Riera-Escamilla A. Genetics of male infertility. Nat Rev Urol 2018;15:369-84.
2. Schlegel PN, Sigman M, Collura B, et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline part I. Fertil Steril 2021;115:54-61.
3. Wosnitzer MS. Genetic evaluation of male infertility. Transl Androl Urol 2014;3:17-26.
4. Krausz C, Riera-Escamilla A, Moreno-Mendoza D, et al. Genetic dissection of spermatogenic arrest through exome analysis: clinical implications for the management of azoospermic men. Genet Med 2020;22:1956-66.
5. Alhathal N, Maddirevula S, Coskun S, et al. A genomics approach to male infertility. Genet Med 2020;22:1967-75.
6. Wang O, Cheng X, Drmanac R, Peters BA. A simple cost-effective method for whole-genome sequencing, haplotyping, and assembly. Methods Mol Biol 2023;2590:101-25.
7. Guo J, Sosa E, Chitiashvili T, et al. Single-cell analysis of the developing human testis reveals somatic niche cell specification and fetal germline stem cell establishment. Cell Stem Cell 2021;28:764-78.e4.
8. Han X, Zhou Z, Fei L, et al. Construction of a human cell landscape at single-cell level. Nature 2020;581:303-9.
9. Zhou Z, Tan C, Chau MHK, et al. TEDD: a database of temporal gene expression patterns during multiple developmental periods in human and model organisms. Nucleic Acids Res 2023;51:D1168-78.
10. Castaneda JM, Shimada K, Satouh Y, et al. FAM209 associates with DPY19L2, and is required for sperm acrosome biogenesis and fertility in mice. J Cell Sci 2021;134:jcs259206.
11. Chen S, An G, Wang H, et al. Human obstructive (postvasectomy) and nonobstructive azoospermia: insights from scRNA-Seq and transcriptome analysis. Genes Dis 2022;9:766-76.
12. Ledig S, Hiort O, Wunsch L, Wieacker P. Partial deletion of DMRT1 causes 46,XY ovotesticular disorder of sexual development. Eur J Endocrinol 2012;167:119-24.
13. Khosronezhad N, Hosseinzadeh Colagar A, Mortazavi SM. The Nsun7 (A11337)-deletion mutation, causes reduction of its protein rate and associated with sperm motility defect in infertile men. J Assist Reprod Genet 2015;32:807-15.
14. Dong Z, Qian J, Law TSM, et al. Mate-pair genome sequencing reveals structural variants for idiopathic male infertility. Hum Genet 2023;142:363-77.

Genetic bases of schizophrenia phenotypes: abridged secondary publication

KCY Wong, ST Rao, S Zhi, PBM Leung, BKW Lee, EFC Cheung, RCK Chan, KKY Ho, KSY Hung, TCK Hui, PC Sham, SSY Lui, HC So *

KEY MESSAGE

Understanding the genetic architecture of schizophrenia phenotypes, shared pathophysiology, and genetic and clinical risk factors associated with disease severity may inform patient classification and guide risk stratification for treatment prioritisation.

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Introduction

Schizophrenia (SCZ) is highly heritable and characterised by wide variability in clinical presentation and prognosis.[1] Genetic factors contribute substantially to this heterogeneity.[2] Understanding the genetic basis is essential for improving diagnosis and treatment. Despite advances in genome-wide association studies (GWAS), the complex aetiology of SCZ remains unclear.[3-5] Most GWAS have focused on the diagnosis itself, without detailed investigation of symptoms, course, and outcomes. Large-scale GWAS involving diverse clinical phenotypes and prognosis in Chinese populations are scarce, limiting identification of specific risk alleles and genes. Furthermore, the extent to which different clinical features and outcomes in SCZ share genetic underpinnings with the core disorder and with other psychiatric conditions remains largely unexplored. This study aimed to investigate the genetic basis of SCZ phenotypes in the Chinese population.

Methods

We analysed a variety of phenotypes, including age at onset, history of self-harm and aggression, and number of psychiatric hospitalisations since onset, using GWAS (with meta-analyses across Chinese and European cohorts), transcriptome-wide association studies, polygenic risk score analysis, gene-set and pathway enrichment analyses, machine learning modelling with Shapley value analysis, and gene-based analytical tools such as MAGMA and MetaXcan.

Results

GWAS identified genome-wide significant single nucleotide polymorphisms (SNPs) associated with age at onset and the number of hospitalisations (both $P<5\times10^{-8}$). A meta-analysis combining Chinese and European cohorts re-identified the same significant SNPs associated with age at onset.

Polygenic risk score analyses revealed significant genetic associations between SCZ phenotypes and other psychiatric disorders. Gene-based analyses and transcriptome-wide association studies implicated specific genes associated with the immune system and brain tissues. Our machine learning model achieved a moderate level of discriminative performance, comparable to that in a previous study,[6] with several predictors identified by Shapley value analysis.

Discussion

The identification of significant SNPs, genes, and biological pathways highlights the importance of specific molecular mechanisms and brain regions in SCZ pathogenesis. These insights may have important implications for risk stratification, such as the early identification of high-risk individuals and guidance for differential diagnosis in ambiguous cases. By elucidating the genetic overlap between SCZ phenotypes and other psychiatric disorders or traits, the present study provides a deeper understanding of the genetic architecture of SCZ and its shared pathophysiology with related phenotypes.

We developed a machine learning model with moderate accuracy to assess the severity of

SCZ phenotypes. This model provides a proof of concept for how combined genetic and clinical risk factors can improve risk stratification and disease subtyping. Such model is particularly relevant for patients with poorer prognosis, who may benefit from prioritised interventions, such as more intensive psychosocial and rehabilitative treatments. Moreover, the analytical frameworks developed to integrate genetic and clinical data in SCZ are broadly applicable to other disorders.

The present study has several limitations. First, the modest sample size may limit statistical power and weaken the reliability of GWAS and polygenic risk score analysis results. The prioritised genetic variants or genes should therefore be considered tentative and require further confirmation in future studies. Second, the use of mismatched ethnic groups in some polygenic risk score estimations may reduce statistical power. Finally, the machine learning model may be biased towards the characteristics of this specific dataset; its generalisability warrants further study. Additional validation in larger and more ethnically diverse samples is required before clinical translation.

Candidate genes identified for clinical phenotypes may serve as useful targets for follow-up functional studies and investigation in other psychiatric disorders. Further research is warranted to identify causal risk factors for SCZ outcomes using Mendelian randomisation, with genetic variants as instruments. Findings on shared genetic bases between SCZ phenotypes and other psychiatric disorders or traits highlight the potential of applying genetics and polygenic risk scores in differential diagnosis. Accurate diagnosis is critical in psychiatry, as treatments and prognosis can differ substantially.

Conclusion

Our study deepens the understanding of the genetic architecture of SCZ phenotypes, shared pathophysiology, and the genetic and clinical risk factors associated with disease severity. Our findings may inform patient classification and guide risk stratification for treatment prioritisation. However, rigorous validation in larger, ethnically diverse cohorts is needed.

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Disclosure

The results of this research have been previously published in:

1. Rao ST, Wong KCY, Zhi S, et al. Unraveling genetic variants underlying schizophrenia phenotypes: an original GWAS in Hong Kong Chinese with cross-ethnic meta-analysis and predictive modeling [preprint]. medRxiv 2025:2025.12.24.25342953.
2. Tubbs JD, Leung PBM, Zhong Y, et al. Pathway-specific polygenic scores improve cross-ancestry prediction of psychosis and clinical outcomes [preprint]. medRxiv 2023:2023.09.01.23294957.
3. Zhan N, Sham PC, So HC, Lui SSY. The genetic basis of onset age in schizophrenia: evidence and models. Front Genet 2023;14:1163361.

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References

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;386:743-800.
2. Fanous AH, Kendler KS. Genetic heterogeneity, modifier genes, and quantitative phenotypes in psychiatric illness: searching for a framework. Mol Psychiatry 2005;10:6-13.
3. Bani-Fatemi A, Graff A, Zai C, Strauss J, De Luca V. GWAS analysis of suicide attempt in schizophrenia: main genetic effect and interaction with early life trauma. Neurosci Lett 2016;622:102-6.
4. Edwards AC, Bigdeli TB, Docherty AR, et al. Meta-analysis of positive and negative symptoms reveals schizophrenia modifier genes. Schizophr Bull 2016;42:279-87.
5. Fanous AH, Zhou B, Aggen SH, et al. Genome-wide association study of clinical dimensions of schizophrenia: polygenic effect on disorganized symptoms. Am J Psychiatry 2012;169:1309-17.
6. Bracher-Smith M, Rees E, Menzies G, et al. Machine learning for prediction of schizophrenia using genetic and demographic factors in the UK biobank. Schizophr Res 2022;246:156-64.

Socio-economic burden and health-related quality of life in patients with rare diseases during the COVID-19 pandemic: abridged secondary publication

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KEY MESSAGES

1. In Hong Kong, total costs for rare disease were estimated to be HK$518 420 per patient per year; >60% of costs were attributable to direct non-healthcare and indirect costs.
2. In Hong Kong, health-related quality of life, in terms of utility score, was significantly lower in patients with rare disease than in patients with other chronic diseases (0.52 vs 0.87-0.88).
3. Higher socio-economic costs for rare diseases were associated with lower utility scores, younger age, shorter duration since diagnosis, and receipt of governmental allowance.
4. During the COVID-19 pandemic, patients and caregivers who reported changes in service or resource utilisation had significantly lower utility scores than those who reported no changes.

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Introduction

Among European populations, rare diseases (RDs) are defined as conditions that affect <50 in 100 000 individuals.[1] Patients with RDs experience complex healthcare challenges and lifelong disabilities, both of which have detrimental impacts on health-related quality of life (HRQoL), which comprises physical, mental, and social well-being, as well as healthcare costs. This study aimed to estimate the socio-economic cost of RDs from a societal perspective, evaluate the HRQoL of patients with RDs and their caregivers, identify factors associated with RD cost and HRQoL, and evaluate the impact of COVID-19 on the socio-economic burden and HRQoL of RDs.

Methods

This prospective cross-sectional study was carried out between March and October 2020 during the COVID-19 pandemic. Patients with RDs or their caregivers were recruited. The validated Client Service Receipt Inventory for the RD population was used to collect demographic and resource utilisation data.[2] A prevalence-based bottom-up approach was implemented to quantify service and resource utilisation from a societal perspective. Direct healthcare costs (health services, medications, medical resources/consumables, community medical services) and direct non-healthcare costs (professional care, informal care, special education and employment, residential/foster care placements, home modification, transportation) were based on utilisation records, which were valued according to 2022/23 unit costs. Indirect costs were mainly based on labour productivity losses resulting from RD, estimated using the human-capital approach. Territory-wide socio-economic burden was derived by combining the average total annual cost and prevalence of RDs in Hong Kong, based on 2023 year-end population estimates.[3]

The EuroQol 5-Dimension 3-Level (EQ-5D-3L) was used to assess HRQoL in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[4] In cases that patients required a proxy respondent, caregiver HRQoL data were also collected. Utility scores for each patient and caregiver were generated based on the Hong Kong value set and the reverse crosswalk algorithm to facilitate comparison with other studies. The EuroQol visual analogue scale (EQ-VAS) for overall health perception was also used.

Participants were asked whether there was any difference in healthcare and community services/resource utilisation compared with the period prior to the COVID-19 pandemic. Total costs and HRQoL were compared between participants who reported differences in utilisation and those who did not.

Linear regression of independent variables against average annual cost and HRQoL was conducted. Multivariate regression analyses were performed to simultaneously evaluate the association of mean annual costs and HRQoL with different variables. The significance threshold was set at $P<0.05$ (two-tailed).

Results

In total, responses from 325 participants were collected; 41 were excluded due to duplication, insufficient data, or invalid responses. The remaining 284 responses, covering 106 unique RDs, were included in the analysis; 158 responses were patient-completed and 126 were proxy-completed by caregivers.

The mean total cost of RDs was estimated at HK$518 420 per patient per year. The highest cost category was direct non-healthcare costs (39.7%), followed by direct healthcare costs (38.8%) and indirect costs (21.5%) [Table 1]. Direct healthcare costs were estimated at HK$201 114 per patient per year; most were attributed to health services (48.9%) and medications (48.0%). Direct non-healthcare costs were estimated at HK$206 065 per patient per year. Informal care represented 66.7% of total direct non-healthcare costs; 64.4% of patients received care from unpaid caregivers. Among the 88 patients who were receiving education during the study period, 51.1% required schooling in special schools. Indirect costs were estimated at HK$111 240 per patient per year. Patient and caregiver productivity losses represented 31.1% and 67.6% of total indirect costs, respectively. Based on the estimated prevalence of RDs in Hong Kong, the aggregate territory-wide annual cost of RDs was estimated to exceed HK$60.21 billion in 2023.

Regarding patient HRQoL, the mean utility score was 0.52; 30 (10.6%) patients reported negative utility scores. Patients with rare neurological diseases had the lowest mean utility score relative to other patients (0.33 vs 0.64, P<0.001). The mean EQ-VAS score was 66.3. HRQoL data from six other studies across various jurisdictions were pooled with the mean utility score obtained in this study. In total, 12 622 patients with RDs were included; the mean pooled utility score was 0.59 (95% confidence interval=0.52-0.66, I^2=98.65%, Q=187.60, degree of freedom=6, P<0.0001).

Regarding caregiver HRQoL, the mean utility score among 96 caregivers (0.80) was correlated with the patient utility score (r=0.27, P=0.009). The mean EQ-VAS score among 107 caregivers was 73.1.

During the COVID-19 pandemic, 103 (36.3%) patients reported changes in service and resource utilisation compared with the prior period. The mean total cost did not significantly differ between patients who reported changes in utilisation and those who did not (HK$562 802 vs HK$469 246, P=0.294). The mean utility score was lower among patients who reported changes in resource utilisation than among those who reported no such changes (0.38 vs 0.62, P<0.001). Caregivers of patients who reported changes in healthcare and resource utilisation also reported lower utility scores (0.74 vs 0.85, P<0.001).

Lower total RD cost was associated with older age, longer duration since diagnosis, residence in public housing or subdivided flats, and higher patient utility scores (Table 2). The receipt of social security support or governmental allowance was associated with higher total RD costs and lower patient utility scores. Residence in public housing or subdivided flats was associated with a lower utility score among caregivers.

Discussion

In Hong Kong, the societal cost of RDs per patient is >HK$200 000 higher than that of other common diseases, including type 2 diabetes, rheumatoid arthritis, epilepsy, and cerebellar ataxia. The cost of RDs in Hong Kong is comparable to that in other regions in Europe[5] (Table 3). High utilisation of healthcare services is likely driven by the costs of symptomatic therapy and orphan drugs used to treat RDs. Currently, there are insufficient policies to support access to orphan drugs in Hong Kong. A diagnosis of RD is important to reduce unnecessary medical procedures and increase the visibility of patients' conditions within society, thus enabling access to healthcare and social programmes that can potentially reduce the societal cost of RDs. This relationship was supported by our findings, in which the number of years since diagnosis was associated with total cost. In addition to medical challenges, social exclusion contributes to costs by preventing integration of the RD population into the education and employment sectors, which manifests as productivity loss. Although the Disability Discrimination Ordinance was implemented to prevent job inequalities, specific policies are required to address the unique needs of the RD population.

The utility scores of patients (0.52) and caregivers (0.80) were both significantly lower than that of the general population (0.92); they were also lower than scores reported for other chronic diseases, including cancer (0.87) and heart disease (0.88). Patients with neurological RDs had the lowest HRQoL. This may be due to the limited availability of symptomatic therapies for neurological diseases, resulting in persistent mobility problems that cause high levels of pain and discomfort. Patients with 'rare developmental defects during embryogenesis' experienced relatively better HRQoL than other RD categories. These patients were born with disabilities and may not have experienced a change in identity as encountered by patients with acquired conditions. These findings underscore the importance of interventions to promote coping strategies that foster a sense of control over the consequences of disease. Caregiver HRQoL was also lower than that of the general population. This appears to be driven by a high psychological burden, as indicated by more problems related to the anxiety and depression dimension of the EQ-5D-3L, and by intensive

TABLE 1. Direct healthcare cost, direct non-healthcare cost, indirect cost, total cost, and mean utility score of rare diseases (RDs) per patient per year (n=284).

Characteristic	No. (%) of patients	Direct healthcare cost, HK$	Direct non-healthcare cost, HK$	Indirect cost, HK$	Total cost, HK$	Mean ± standard deviation utility score
Sex						
Male	134 (47.2)	140 515	224 051	125 325	489 891	0.51±0.37
Female	150 (52.8)	255 250	189 998	98 658	543 906	0.54±0.34
Age, y						
≤18	88 (31.0)	355 059	417 501	126 914	899 474	0.46±0.41
19-64	185 (65.1)	132 896	111 640	103 806	348 342	0.57±0.32
≥65	11 (3.9)	116 857	102 639	110 888	330 384	0.32±0.30
RD category (seven patients had two different RDs)						
Rare bone disease	17 (6.0)	257 905	324 862	54 144	636 910	0.65±0.25
Rare developmental defects during embryogenesis	67 (23.6)	77 464	301 165	117 388	496 017	0.63±0.30
Rare endocrine disease	4 (1.4)	78 829	49 138	101 475	229 442	0.67±0.24
Rare eye disease	4 (1.4)	5 773	161 928	223 568	391 269	0.73±0.17
Rare gastroenterological disease	2 (0.7)	339 195	237 680	237 600	814 475	0.41±0.19
Rare haematological disease	9 (3.2)	1 101 056	107 224	129 188	1 337 468	0.81±0.18
Rare immune disease	6 (2.1)	19 694	38 559	0	58 253	0.76±0.32
Rare inborn errors of metabolism	31 (10.9)	448 828	327 657	110 995	887 479	0.45±0.50
Rare neoplastic disease	3 (1.1)	47 705	307 064	63 478	418 248	0.82±0.15
Rare neurological disease	107 (37.7)	184 575	165 124	130 026	479 726	0.33±0.31
Rare respiratory disease	8 (2.8)	150 536	42 903	143 028	336 467	0.55±0.17
Rare skin disease	4 (1.4)	35 306	3 577	71 487	110 370	0.67±0.13
Rare systemic or rheumatological disease	24 (8.5)	60 000	52 788	48 704	161 492	0.80±0.17
No. of other family members with RDs (some data missing)						
0	201 (70.8)	246 231	224 389	112 500	583 120	0.48±0.37
1	35 (12.3)	52 133	201 531	118 898	372 561	0.65±0.29
2	16 (5.6)	34 667	44 821	139 668	219 156	0.56±0.23
3	6 (2.1)	110 976	118 533	85 416	314 925	0.51±0.27
4	8 (2.8)	50 251	240 830	63 530	354 611	0.53±0.53
≥5	7 (2.5)	27 674	60 196	3 552	91 422	0.79±0.30
Years since diagnosis (some data missing)						
0-5	103 (36.3)	334 873	259 139	126 654	720 666	0.48±0.38
6-10	34 (12.0)	106 031	248 683	129 648	484 361	0.50±0.39
11-15	30 (10.6)	261 520	184 315	124 596	570 431	0.62±0.29
16-20	28 (9.9)	78 375	167 165	111 889	357 429	0.57±0.35
21-25	26 (9.2)	52 213	188 074	94 103	334 390	0.53±0.36
26-30	13 (4.6)	62 061	143 849	68 964	274 874	0.46±0.36
>30	13 (4.6)	59 101	135 459	99 603	294 164	0.42±0.39
Education/employment status (some data missing)						
Student	88 (31.0)	227 807	399 106	107 617	734 530	0.53±0.39
Full-time employment	49 (17.3)	134 348	44 278	42 635	221 261	0.73±0.24
Part-time employment	14 (4.9)	401 474	56 130	63 733	521 337	0.53±0.24
Housewife/househusband	16 (5.6)	55 709	84 264	148 785	288 758	0.45±0.22
Retired	25 (8.8)	83 267	60 611	144 654	288 531	0.45±0.29
Not receiving education/unemployed	70 (24.6)	284 494	205 688	168 285	658 466	0.39±0.38
Type of housing (some data missing)						
Public housing/subdivided flats	122 (43.0)	76 279	184 038	113 854	374 172	0.45±0.33
Rented flat	36 (12.7)	379 437	219 749	111 058	710 244	0.57±0.41
Owned flat	114 (40.1)	291 621	225 472	108 036	625 128	0.60±0.35
Other	11 (3.9)	82 347	195 890	126 167	404 405	0.46±0.39
Social security support/governmental allowance						
Yes	174 (61.3)	269 181	249 789	134 873	653 803	0.45±0.35
No	110 (38.7)	93 445	136 966	73 857	304 268	0.64±0.34
Service/resource utilisation during COVID-19 pandemic (some data missing)						
Affected	103 (36.3)	184 132	240 150	138 521	562 802	0.38±0.38
No difference	157 (55.3)	180 602	185 293	103 351	469 246	0.62±0.30
Total	**284 (100.0)**	**201 114**	**206 065**	**111 240**	**518 420**	**0.52±0.36**

TABLE 2. Independent factors associated with total cost, patient utility score, and caregiver utility score.

Factor	Total cost, HK$		Patient utility score		Caregiver utility score	
	Adjusted coefficient (95% confidence interval)	Adjusted P value	Adjusted coefficient	Adjusted P value	Adjusted coefficient	Adjusted P value
Older age	-8254 (-13 156 to -3 352)	0.001	<0.001	0.891	-0.002	0.050
Female sex	113 058 (-69 799 to 295 915)	0.224	0.030	0.519	0.030	0.275
Longer duration since diagnosis	-9308 (-18 546 to -69)	0.048	0.002	0.473	0.002	0.200
Higher number of family members with rare diseases	-35 392 (-103 012 to 32 227)	0.303	0.017	0.308	0.008	0.574
Residence in public housing/subdivided flats	-289 481 (-476 905 to -102 058)	0.003	-0.089	0.059	-0.109	<0.001
Receipt of social security support/ governmental allowance	241 605 (41 627 to 441 582)	0.018	-0.196	<0.001	-0.055	0.095
Higher patient utility score	-485 183 (-747 209 to -223 157)	<0.001	-	-	-	-

caregiving responsibilities leading to productivity losses. Programmes and policies for patients with RDs should consider empowering and supporting caregivers.

The COVID-19 pandemic did not significantly affect the total cost of RDs, potentially due to the essential medical needs of affected patients. In contrast, the utility scores of patients with RDs and their caregivers were significantly lower among those who reported differences in healthcare and resource use during the pandemic. Limited access to healthcare services during this period might have generated uncertainty regarding disease management, negatively affecting psychological well-being. The detrimental impact of the pandemic on costs and HRQoL highlights the importance of maintaining effective RD management during public health crises.

This study highlights the unique needs of patients with RDs, particularly during health emergencies. Interventions for the RD population should address multiple dimensions of disease impact through a patient-centred and multidisciplinary approach. Civil society groups and governments play important roles in facilitating the implementation of appropriate legislation and policies.

This study has several limitations. First, recruitment was voluntary, and the study population may not be representative of the RD population in Hong Kong. Second, detailed subgroup analyses comparing costs and HRQoL across RD categories were not feasible due to limited data in certain groups. Third, the EQ-5D-3L measure of HRQoL may not be generalisable to paediatric patients; however, the proxy version has been validated. Finally, caregiver HRQoL results may only be representative of patients who were unable to complete the questionnaire independently.

TABLE 3. Total costs of rare diseases (RDs) from a societal perspective in different regions.

Region[5]	No. of RDs included	Year of publication, year of cost estimation	Total cost of RDs per patient per year, HK$ adjusted to 2022/23 prices
Bulgaria	8	2016, 2012	183 254
France	10	2016, 2012	340 007
Germany	9	2016, 2012	743 899
Hungary	8	2016, 2012	177 188
Italy	10	2016, 2012	487 927
Spain	9	2016, 2012	459 425
Sweden	10	2016, 2012	483 850
United Kingdom	9	2016, 2012	450 752
United States	379	2022, 2019	499 923
Germany, France, and Italy	23	2023, 2021	1 001 542
Turkey	>7	2023, 2020	26 124
Germany	3	2023, 2019	1 678 255
Hong Kong	106	2023	518 420

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2. Chung CCY, Ng NYT, Ng YNC, et al. Socio-economic costs of rare diseases and the risk of financial hardship: a cross-sectional study. Lancet Reg Health West Pac 2023;34:100711.

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References

1. World Health Organization. Priority diseases and reasons for inclusion 2013. Accessed December 2025. Available from: https://www.who.int/medicines/areas/priority_medicines/Ch6_19Rare.pdf
2. Chung CCY, Fung JLF, Lui ACY, et al. Client Service Receipt Inventory as a standardised tool for measurement of socio-economic costs in the rare genetic disease population (CSRI-Ra). Sci Rep 2021;11:23837.
3. Chiu ATG, Chung CCY, Wong WHS, Lee SL, Chung BHY. Healthcare burden of rare diseases in Hong Kong: adopting ORPHAcodes in ICD-10 based healthcare administrative datasets. Orphanet J Rare Dis 2018;13:147.
4. Wong ELY, Ramos-Goni JM, Cheung AWL, Wong AYK, Rivero-Arias O. Assessing the use of a feedback module to model EQ-5D-5L health states values in Hong Kong. Patient 2018;11:235-47.
5. Lopez-Bastida J, Oliva-Moreno J, Linertova R, Serrano-Aguilar P. Social/economic costs and health-related quality of life in patients with rare diseases in Europe. Eur J Health Econ 2016;17(Suppl 1):1-5.

Mirror therapy and transcutaneous electrical nerve stimulation to improve upper limb function in patients with stroke: abridged secondary publication

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KEY MESSAGE

Mirror therapy combined with bilateral transcutaneous electrical nerve stimulation appears to be superior to sham mirror therapy plus nerve stimulation in improving upper limb motor function and community integration among people with subacute or chronic stroke. The effects were maintained at 4 weeks after treatment ended.

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Introduction

Approximately 70% to 80% of people with stroke have motor deficits in their upper extremities, and approximately 30% to 66% of them do not regain functional use of their paretic arm within 6 months after stroke.[1] Impairment of upper limb function hinders activities of daily living such as eating and personal care.

Bilateral transcutaneous electrical nerve stimulation (Bi-TENS) was applied to both the paretic and non-paretic limbs,[2,3] and mirror therapy (MT), in which patients view a reflection of the moving intact limb, can enhance recovery of motor function in paretic limbs after stroke.[4,5] Both TENS and MT can induce neuroplastic changes that enhance the motor system; they may act synergistically to support motor practice.

This study aimed to compare the effects of MT plus Bi-TENS versus sham MT plus Bi-TENS in promoting the recovery of upper limb motor function in people with stroke.

Methods

Older adults aged 55 to 85 years with first-ever stroke within 5 years who had residual upper limb impairment but retained minimal active movement and sufficient cognitive function were invited to participate. Participants were randomly allocated to receive either MT plus Bi-TENS or sham MT plus Bi-TENS, in addition to usual care. The intervention consisted of 16 sessions delivered twice weekly over 8 weeks. During MT, an adjustable-angle frame with a mirror box was positioned in front of participants. The paretic arm was positioned behind the mirror, and the intact arm was positioned facing the reflective surface. Concurrently, participants received TENS (100 Hz with 0.2 ms square pulses, at an intensity barely below the motor threshold) over the median and radial nerves of both intact and paretic arms while practising symmetrical bilateral upper limb exercises. Participants were reminded to focus on the illusion that the reflected arm was the paretic limb. Exercises included elbow flexion and extension, forearm supination and pronation, wrist flexion and extension, radial and ulnar deviation of the wrist, finger opposition, and gripping. During sham MT, the mirror surface was covered to remove the visual illusion.

Participants were assessed at baseline, 4 weeks (after 8 sessions), 8 weeks (after 16 sessions), and at a 4-week follow-up visit. Primary outcomes included motor impairment of the paretic upper limb, assessed using the Fugl-Meyer Assessment of Upper Extremity (FMA-UE) and upper limb motor function using the Wolf Motor Function Test (WMFT). Secondary outcomes assessed included proficiency in putting on and removing a long-sleeved jacket using the Jacket Test, frequency and quality of paretic arm use across 30 daily activities using the Motor Activity Log (MAL), perceived participation and the impact of stroke on daily life using the

Stroke Impact Scale 3.0, and level of community integration using the Community Integration Measure (CIM).

All statistical analyses were two-sided; the significance threshold was set at 5%. Data were analysed on an intention-to-treat basis. The two groups were compared using the independent *t* test for continuous variables and Chi-squared test for categorical variables. Mixed-effects models were used to examine group differences in changes in outcomes across assessment time points.

Results

In total, 30 participants with subacute stroke (3-11 weeks post-stroke) and 60 participants with chronic stroke (within 5 years post-stroke) were recruited. Participants with subacute stroke received 3 hours of standardised conventional physiotherapy and occupational therapy in addition to the intervention, whereas participants with chronic stroke received the intervention alone due to the COVID-19 pandemic. Consequently, participants with subacute and chronic stroke were analysed separately.

In the subacute stroke group, MT plus Bi-TENS was associated with greater motor recovery (FMA-UE), better upper limb motor function (WMFT), improved performance on a functional dressing task (Jacket Test), higher self-reported frequency and quality of paretic arm use in daily life (MAL), and higher levels of community integration (CIM). These improvements were maintained at the 4-week follow-up, suggesting lasting benefits.

In the chronic stroke group, MT plus Bi-TENS showed greater improvements in upper limb impairment (FMA-UE) and upper limb motor function (WMFT). The magnitude of change was typically smaller than that observed in the subacute stroke group.

Discussion

Among participants with subacute or chronic stroke, MT plus Bi-TENS had synergistic effects and resulted in significantly greater increases in FMA-UE and WMFT scores compared with sham MT plus Bi-TENS. Bi-TENS has been reported to improve motor function of the paretic upper and lower limbs, probably due to additional sensory input from the non-paretic side, which reduces paresis on the paretic side by rebalancing interhemispheric inhibition, activating homologous neural networks in the intact and lesioned hemispheres, and recruiting neural networks of the intact hemisphere.[2,3]

MT can improve upper extremity motor function and activities of daily living in people after stroke.[4] Its mechanisms are multifactorial. Visual input during MT may substitute for reduced proprioceptive input and increase spatial attention to the paretic limb, thereby improving motor function.[4,5] These improvements may be mediated by increased cortical activity in the lesioned hemisphere and activation of the mirror neuron system.[4,5]

The greatest improvements in post-stroke motor function occur 3 to 6 weeks after stroke onset,[1] although interventions can also improve motor function years after stroke onset.[2,3] Further studies are warranted to determine mechanisms of motor recovery across post-stroke phases, including differences in cortical reorganisation, kinematic changes, and other aspects of clinical improvement.

Conclusion

Compared with sham MT plus Bi-TENS, MT plus Bi-TENS achieved greater increases in FMA-UE, WMFT, Jacket Test, and CIM scores among participants with subacute or chronic stroke. The effects were maintained at 4 weeks after treatment ended.

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References

1. Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke patients: the Copenhagen Stroke Study. Arch Phys Med Rehabil 1994;75:394-8.
2. Chen P, Liu TW, Kwong PWH, et al. Bilateral transcutaneous electrical nerve stimulation improves upper limb motor recovery in stroke: a randomized controlled trial. Stroke 2022;53:1134-40.
3. Kwong PWH, Ng GYF, Chung RCK, Ng SSM. Bilateral transcutaneous electrical nerve stimulation improves lower-limb motor function in subjects with chronic stroke: a randomised controlled trial. J Am Heart Assoc 2018;7:e007341.
4. Thieme H, Morkisch N, Mehrholz J, et al. Mirror therapy for improving motor function after stroke. Cochrane Database Syst Rev 2018;7:CD008449.
5. Toh SF, Fong KN. Systematic review on the effectiveness of mirror therapy in training upper limb hemiparesis after stroke. Hong Kong J Occup Ther 2012;22:84-95.

Fine needle biopsy guided by contrast-enhanced harmonic versus conventional endoscopic ultrasound with macroscopic on-site evaluation for solid pancreatic lesions: abridged secondary publication

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KEY MESSAGES

1. Fine needle biopsy guided by either contrast-enhanced harmonic or conventional endoscopic ultrasound, with macroscopic on-site evaluation of specimen adequacy, achieves similarly low false-negative rates and high diagnostic accuracies when the prevalence of avascular areas in lesions is <31%.
2. Routine use of contrast-enhanced harmonic endoscopic ultrasound for fine needle biopsy may be unnecessary when dedicated needles are used for tissue acquisition and the expected prevalence of avascular areas is low in target lesions.

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Introduction

Fine needle aspiration (FNA) is the first-line diagnostic method, especially when rapid on-site evaluation by a cytopathologist is available.[1] However, FNA has limitations, including inadequate cellular acquisition and inability to provide core tissue for histological analysis.[1] Additionally, rapid on-site evaluation may be unavailable due to limited resources.

Endoscopic ultrasound (EUS)–guided fine needle biopsy (FNB) has been used to improve tissue acquisition.[1] FNB needles can collect both cells and intact core tissue for histological analysis. Macroscopic on-site evaluation (MOSE) is increasingly used to assess specimen adequacy[2] based on the presence of a macroscopic visible core (MVC), defined as whitish or yellowish tissue with an apparent bulk. EUS-guided FNB combined with MOSE provides comparable diagnostic accuracy and better tissue quality, while requiring fewer passes, relative to FNB alone.[2] Nevertheless, the reported false-negative rate is 21.3%, likely due to tumour necrosis in sizeable tumours.[2] Contrast-enhanced EUS allows better delineation of vascularity and tissue perfusion.[3] Contrast-enhanced harmonic EUS (CH-EUS) facilitates FNB of pancreatic lesions and helps avoid necrotic tissue and/or vascular structures within lesions.[3]

Puncturing avascular or necrotic areas of a tumour is a major cause of false-negative results. CH-EUS can define avascular or necrotic areas within a tumour, which may improve diagnostic accuracy. This study aimed to compare the diagnostic performance of FNB guided by either CH-EUS or conventional EUS, along with MOSE, for solid pancreatic lesions.

Methods

This prospective randomised controlled study was conducted between February 2022 and August 2023 at three tertiary referral centres in Hong Kong, Italy, and Korea. Consecutive patients aged 18 to 80 years referred for EUS-guided tissue acquisition for solid pancreatic lesions >1 cm were screened for eligibility.

Patients with coagulopathy, altered anatomy, contraindications to endoscopy, or pregnancy were excluded. Eligible patients were randomised in a 1:1 ratio to undergo FNB guided by either CH-EUS or conventional EUS.

Each pancreatic lesion was examined using a linear echoendoscope. EUS-guided tissue acquisition was performed with a 22-gauge Franseen FNB needle. The degree of suction was selected by the endoscopist. MOSE was used to assess specimen adequacy. In the CH-EUS group, CH-EUS with SonoVue was used to identify non-enhancing, avascular (necrotic) areas in the target lesion and to guide FNB to viable areas. FNB was deemed complete if the obtained MVC was ≥4 mm. If the MVC was <4 mm, FNB was repeated until a total MVC length ≥4 mm was achieved. Up to seven passes were allowed.

The primary outcome was the false-negative rate. Secondary outcomes were sensitivity, specificity, positive predictive value, negative predictive value, procedural time, and procedure-related complications.

Results

In total, 128 patients were randomised to undergo FNB guided by CH-EUS (n=64) or conventional EUS (n=64). The two groups were comparable in terms of baseline characteristics, except for the rate of pancreatic adenocarcinoma (59.4% vs 79.7%, P=0.013; Table). Avascular areas were detected in 25.0% of solid pancreatic lesions in the CH-EUS group and in 20.3% of such lesions in the conventional EUS group; detection increased to 31.3% with CH-EUS. The two groups were similar in terms of the number of passes required to achieve an MVC length ≥4 mm (1 vs 1.5) and the mean MVC length (16.8 vs 20.6 mm). Procedure time was longer in the CH-EUS group (28.9 vs 24.4 minutes, P=0.039). Procedure-related adverse event rates were low (1.6% in both groups).

For CH-EUS–guided FNB and conventional EUS–guided FNB, respectively, false-negative rates were 6.0% and 7.9%; sensitivities were 94.0% and 92.1%; specificities were 100% and 100%; and diagnostic accuracies were 95.3% and 92.2% (Table).

Discussion

Although CH-EUS increased the detection of avascular areas in solid pancreatic lesions from 25.0% to 31.3%, the false-negative rates of both CH-EUS–guided FNB and conventional EUS–guided FNB remained comparable (6.0% vs 7.9%), consistent with single-centre randomised controlled studies from Korea and Taiwan.[4,5] In the Korean study involving 240 patients, diagnostic sensitivities for malignancy were 85.8% and 88.3% for the respective FNB approaches.[4] Of note, the needle types used were heterogeneous.[4] This may have contributed to the slightly lower sensitivity. In the Taiwan study, 118 patients with solid pancreatic lesions underwent FNB guided by either CH-EUS or conventional EUS using the fanning technique.[5] There was no difference in diagnostic sensitivity (100% vs 100%) or accuracy (98.3% vs 100%).

Data regarding the false-negative rate of EUS-guided tissue acquisition using dedicated FNB needles remain scarce. Both studies from Korea and Taiwan discussed the false-negative rate of CH-EUS–guided FNB. In our prior study,[2] the false-negative rate of EUS-guided tissue acquisition using a 19-gauge conventional FNA needle was 21.3%. In contrast, the current study demonstrated false-negative rates of 6.0% and 7.9% when a dedicated 22-gauge FNB needle was used. These findings suggest that routine use of CH-EUS does not further reduce the false-negative rate when a dedicated FNB needle is used and when the prevalence of avascular areas in target lesions is <31%.

The present study has several limitations. First, the actual magnitude of effect of each modality is unknown. It is possible that the superior tissue acquisition achieved with modern dedicated FNB needles eclipsed the potential benefit of CH-EUS.[3-5] Given that dedicated FNB needles have been increasingly adopted, it may be unethical to conduct a comparative study of CH-EUS–guided FNA versus CH-EUS–guided FNB. Second, it remains uncertain how the prevalence and extent of avascular areas (necrosis) affect the false-negative rate. Although the prevalence of avascular areas within solid pancreatic lesions in our study was 31%—higher than the 16.4% reported in another study,[3] our study may have been underpowered to detect a small difference in false-negative rates between techniques. Third, a higher frequency of pancreatic adenocarcinoma was observed in the conventional EUS group. The use of a separate patient randomisation website for each study centre is likely to reduce potential bias associated with unbalanced pathological diagnoses between study groups.

Conclusion

Both CH-EUS–guided and conventional EUS–guided FNB demonstrate low false-negative rates and high diagnostic accuracies for solid pancreatic lesions. Routine use of CH-EUS may be unnecessary when the prevalence of avascular areas in target lesions is low.

Funding

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TABLE. Participant characteristics and diagnostic performance of fine needle biopsy guided by either conventional endoscopic ultrasound (EUS) or contrast-enhanced harmonic EUS (CH-EUS).

Variable	All (n=128)*	Conventional EUS (n=64)*	CH-EUS (n=64)*	P value
Age, y	66.5±10.1	67.6±9.7	65.4±10.4	0.231
Male sex	60 (46.9)	34 (53.1)	26 (40.6)	0.156
Lesion size, mm	32.3±13.5	34.0±13.4	30.7±13.5	0.168
Lesion location				
Uncinate process	12 (9.4)	5 (7.8)	7 (10.9)	0.510
Head	52 (40.6)	31 (48.4)	21 (32.8)	
Neck	13 (10.2)	6 (9.4)	7 (10.9)	
Body	28 (21.9)	12 (18.8)	16 (25.0)	
Tail	23 (18.0)	10 (15.6)	13 (20.3)	
Lesion echogenicity				
Hypoechoic	124 (96.9)	63 (98.4)	61 (95.3)	0.619
Hyperechoic	0	0	0	
Isoechoic	4 (3.1)	1 (1.6)	3 (4.7)	
Contrast enhancement pattern				
Hypoenhanced	-	-	37 (57.8)	-
Hyperenhanced	-	-	18 (28.1)	-
Isoenhanced	-	-	9 (14.1)	-
Avascular areas identified on B-mode EUS	29 (22.7)	13 (20.3)	16 (25.0)	0.526
Avascular areas identified on CH-EUS	-	-	20 (31.3)	-
Final diagnosis				
Pancreatic adenocarcinoma	89 (69.5)	51 (79.7)	38 (59.4)	0.013
Pancreatic neuroendocrine tumour	15 (11.7)	7 (10.9)	8 (12.5)	0.783
Metastatic cancer to the pancreas	5 (3.9)	3 (4.7)	2 (3.1)	>0.999
Lymphoma	1 (0.8)	0	1 (1.6)	>0.999
Solid pseudopapillary tumour	1 (0.8)	1 (1.6)	0	>0.999
Intraductal papillary mucinous neoplasm with high-grade dysplasia	2 (1.6)	1 (1.6)	1 (1.6)	>0.999
Intraductal papillary mucinous neoplasm with low-grade dysplasia	1 (0.8)	0	1 (1.6)	>0.999
Serous cystadenoma	3 (2.3)	0	3 (4.7)	0.244
Focal chronic pancreatitis	4 (3.1)	0	4 (6.3)	0.119
Autoimmune pancreatitis	3 (2.3)	1 (1.6)	2 (3.1)	>0.999
Others	4 (3.1)	0	4 (6.3)	0.119
Puncture approach				0.077
Transgastric	-	27 (42.2)	37 (57.8)	
Transduodenal	-	37 (57.8)	27 (42.2)	
No. of passes	-	1.5 (1-2)	1 (1-2)	0.480
Macroscopic visible core length, mm	-	20.6±21.0	16.8±15.9	0.259
False-negative rate, %	-	7.9	6.0	>0.999
Sensitivity, %	-	92.1	94.0	>0.999
Specificity, %	-	100.0	100.0	>0.999
Positive predictive value, %	-	100.0	100.0	>0.999
Negative predictive value, %	-	16.7	82.4	0.009
Diagnostic accuracy, %	-	92.2	95.3	0.718

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

Disclosure

The results of this research have been previously published in:

1. Chong CCN, Ligresti D, Kim TH, et al. Contrast enhanced EUS versus conventional EUS guided fine needle biopsy with macroscopic on-site evaluation for solid pancreatic lesions: a multicenter randomized trial. Gastrointest Endosc 2025:S0016-5107(25)02114-5.
2. Chong CC, Pittayanon R, Pausawasdi N, et al. Consensus statements on endoscopic ultrasound-guided tissue acquisition. Guidelines from the Asian Endoscopic Ultrasound Group. Dig Endosc 2024;36:871-83.

References

1. van Riet PA, Erler NS, Bruno MJ, Cahen DL. Comparison of fine-needle aspiration and fine-needle biopsy devices for endoscopic ultrasound-guided sampling of solid lesions: a systemic review and meta-analysis. Endoscopy 2021;53:411-23.
2. Chong CCN, Lakhtakia S, Nguyen N, et al. Endoscopic ultrasound-guided tissue acquisition with or without macroscopic on-site evaluation: randomized controlled trial. Endoscopy 2020;52:856-63.
3. Kamata K, Takenaka M, Omoto S, et al. Impact of avascular areas, as measured by contrast-enhanced harmonic EUS, on the accuracy of FNA for pancreatic adenocarcinoma. Gastrointest Endosc 2018;87:158-63.
4. Cho IR, Jeong SH, Kang H, Kim EJ, Kim YS, Cho JH. Comparison of contrast-enhanced versus conventional EUS-guided FNA/fine-needle biopsy in diagnosis of solid pancreatic lesions: a randomized controlled trial. Gastrointest Endosc 2021;94:303-10.
5. Kuo YT, Chu YL, Wong WF, et al. Randomized trial of contrast-enhanced harmonic guidance versus fanning technique for EUS-guided fine-needle biopsy sampling of solid pancreatic lesions. Gastrointest Endosc 2023;97:732-40.

Cryosurgery for early breast cancers: abridged secondary publication

A Kwong, THM Co *, E Fukuma, PL Khong, T Shek, G Lo, G Ho

KEY MESSAGES

1. After cryosurgery for early breast cancers, residual cancer is likely to occur at the periphery of the cryoablation site.
2. Careful preoperative planning and intra-operative monitoring are crucial to ensure complete cryoablation.

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Introduction

Breast cancer is a leading cause of cancer-related death in women. Increased awareness and improved imaging technology and screening have led to earlier cancer detection and improved survival rates.[1]

Surgical removal of breast cancer remains the gold standard of treatment. Endoscopic, robotic-assisted, or ablative surgery enables quicker postoperative recovery, shorter hospital stays, smaller wounds, and improved cosmetic outcomes. Techniques for minimally invasive percutaneous ablation include cryoablation, radiofrequency ablation, and laser ablation.[2]

Cryoablation is performed under local anaesthesia and is associated with minimal pain.[3] It can be an alternative to surgery for patients who are unsuitable for surgical treatment due to contraindications, particularly those with comorbidities that increase the risk of perioperative complications.

A previous study in Japan comprised the largest series of cryosurgery for early luminal breast cancers measuring ≤15 mm.[4] The present study aimed to evaluate the safety, feasibility, and efficacy of percutaneous cryoablation for luminal and non-luminal early breast cancers.

Methods

Patients with biopsy-proven T1 breast cancers or ductal carcinoma in situ were screened for eligibility for cryosurgery. Those with solitary T1 breast cancers of any immunohistotype, with a tumour-to-skin surface distance >5 mm, were included. Patients with invasive lobular carcinoma or lobular carcinoma in situ, pregnancy or lactation, or retroareolar tumours were excluded. Eligible patients received counselling regarding treatment options: cryosurgery followed by standard breast-conserving surgery or conventional surgical treatment with or without axillary surgery. Patients who opted for cryosurgery were recruited.

Pre-cryoblation magnetic resonance imaging of the breasts was performed to exclude multicentric tumours and to accurately estimate tumour size. Positron emission tomography–computed tomography was performed to corroborate the findings. Patients with multifocal or multicentric tumours, or tumour size >2 cm, were excluded. All images were reviewed by a radiologist and a nuclear medicine physician.

Cryosurgery was performed using the IceCure ProSense Cryoablation System. Preoperative ultrasound was used to localise the index tumour. The cryoprobe was inserted through the epicentre of the tumour; cryosurgery was performed according to the protocol. Intra-operative monitoring of ice-ball formation was undertaken. Cryosurgery was considered complete when a circumferential margin of 14 mm was achieved. Axillary surgery (such as sentinel node biopsy or axillary dissection) was performed where appropriate.

Post-cryoablation imaging was performed at 6 weeks. Lumpectomy of the cryoablated tumour was performed at 8 weeks. Intra-operative ultrasound was used to assess the cryoablated tumour, and a circumferential margin of at least 1 cm was excised for histopathological assessment. Specimens were sent for evaluation of cryoablation completeness. The primary endpoint was the complete ablation rate (%); secondary endpoints included risk factors for incomplete ablation and complication rates (%).

Results

Of 22 patients recruited, seven were excluded due to tumour size >20 mm. The remaining 15 patients underwent cryosurgery under general anaesthesia followed by lumpectomy and breast-conserving surgery. Their median age was 53 (range, 40-67) years. Five patients had ductal carcinoma in situ,

whereas 10 patients had invasive ductal carcinoma (IDC). Among the latter, five had luminal-type cancers (three luminal A and two luminal B), three had HER2-enriched invasive carcinoma, and two had triple-negative IDC. The 10 patients with IDC also underwent sentinel node biopsy. None had clinical or radiological nodal metastases. Median tumour sizes (largest dimension) were 13 mm (range, 8.6-18 mm) on ultrasound and 16 mm (range, 10-20 mm) on magnetic resonance imaging; ultrasound slightly underestimated tumour size.

The median cryoablation time (freeze-thaw cycle) was 75 (range, 25-101) minutes. Ten patients received two cycles to achieve the desired ice-ball size, whereas five patients received ≥3 cycles. The median ice-ball size was 44.5×44.5×45.2 (range, 35×37×36 to 58.5×60×60) mm.

In the lumpectomy specimen, seven patients had residual cancer: six with residual IDC and one with residual ductal carcinoma in situ. All residual cancers were identified at the periphery of cryoablated breast tissue. Ischaemic necrosis and fat necrosis were observed in other areas. Cell viability and immunohistochemistry tests did not reveal viable cancer cells at the centre of the cryoablated tumour in any of the 15 patients.

Among the seven patients with residual cancer, six had IDC: triple-negative IDC (n=1), HER2-enriched IDC (n=1), and luminal cancers (n=4). Among the six patients with IDC, three had a Ki-67 index ≥18%; tumour sizes were ≤15 mm in four and >15 mm in two. Among the seven patients with residual cancer, the median three-dimensional sonographic tumour size was 13.5×13.7×12.7 (range, 10.5×9.3×6.6 to 14×12.6×15) mm. Among the eight patients without residual cancer, the median sonographic tumour size was 11×11.6×9.5 (range, 11.2×8×8.6 to 17.5×16.4×17.1) mm.

Residual cancer after cryoablation was not associated with histotype, tumour size, Ki-67 index, ice-ball size, procedure duration, or number of cryosurgery cycles. All tumours were completely ablated centrally. No patients developed postoperative complications such as frost injury, bleeding, or haematoma.

Discussion

Cryosurgery is effective in treating small (≤15 mm) luminal-type breast cancers.[4] Cryoablation is achieved through freeze-thaw cycles, leading to tumour cell death and destruction of the vasculature. The initial results of cryosurgery at our institution were less than satisfactory, with a residual cancer rate of up to 46.7%, reflecting a steep learning curve.

None of the tumour- or surgery-related factors was associated with an increased risk of residual cancer after cryoablation. There was a trend towards a higher residual cancer rate in tumours >15 mm than in tumours ≤15 mm (42.9% vs 12.5%); however, this difference did not reach statistical significance, likely due to the small sample size. The three-dimensional size of the tumour should be considered.

Our findings suggest the presence of a learning curve for cryosurgery. Appropriate pre-treatment surgical planning is vital. The operating surgeon should fully understand the orientation of the tumour and its relationship to ice-ball formation, which is oval rather than spherical. It is crucial that the cryoprobe is inserted along the long axis of the tumour. Estimation of the number of freezing cycles required is fundamental to successful cryosurgery. The ice-ball must be sufficiently large to encompass the entire tumour with an adequate margin.

Conclusion

Given the higher residual cancer rate in tumours >15 mm, cryosurgery for these tumours is not recommended. Cryosurgery may potentially be applied to breast cancer types other than luminal breast cancer.

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Disclosure

The results of this research have been previously published in:

1. Kwong A, Co M, Fukuma E. Prospective clinical trial on expanding indications for cryosurgery for early breast cancers. Clin Breast Cancer 2023;23:363-8.

References

1. Kaufman CS. Cryoablation for breast cancer: is it time? Breast Dis Year Book Q 2005;16:227-9.
2. Nguyen T, Hattery E, Khatri VP. Radiofrequency ablation and breast cancer: a review. Gland Surg 2014;3:128-35.
3. Manenti G, Scarano AL, Pistolese CA, et al. Subclinical breast cancer: minimally invasive approaches. Our experience with percutaneous radiofrequency ablation vs. cryotherapy. Breast Care (Basel) 2013;8:356-60.
4. Adachi T, Machida Y, Fukuma E, Tateishi U. Fluorodeoxyglucose positron emission tomography/computed tomography findings after percutaneous cryoablation of early breast cancer. Cancer Imaging 2020;20:49.

Acceptance and commitment therapy–based asthma management programme for parents of children with asthma and attention-deficit hyperactivity disorder: abridged secondary publication

YY Chong *, WT Chien, K Fung, CHA Poon, SP Leung, SY Lam

KEY MESSAGES

1. An acceptance and commitment therapy–based asthma management programme for parents of children with asthma and attention-deficit hyperactivity disorder resulted in significant reductions in unplanned healthcare visits and significant improvements in asthma control and attention-deficit hyperactivity disorder symptom severity at 12 months post-intervention.
2. Parents showed improvements in psychological adjustment, asthma management self-efficacy, psychological flexibility, parenting competence, and overall family functioning across the 12-month follow-up period.
3. Qualitative feedback from parents affirmed the practicality and appropriateness of the intervention.

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Introduction

Asthma and attention-deficit hyperactivity disorder (ADHD) are common paediatric conditions. Children with asthma are 1.6 times more likely to develop ADHD.[1] The underlying mechanisms may involve inflammatory processes and immune dysregulation, affecting neurodevelopment and sleep. In Hong Kong, there has been a notable increase in the use of psychiatric services for ADHD among children with asthma.[2,3]

Children affected by both asthma and ADHD are more likely to require emergency care for asthma exacerbations. Heightened parental stress and increased risks of parental depressive and anxiety disorders may compromise effective asthma management. ADHD-associated executive function deficits present further challenges to asthma management, thereby requiring greater parental engagement and communication. Asthma education and parenting programmes often overlook the psychological aspects of parenting. A Cochrane review highlighted the ineffectiveness of family therapy and problem-solving therapy in improving parental psychological health or child asthma outcomes.[4]

Acceptance and commitment therapy (ACT), a mindfulness-based cognitive behavioural therapy, has demonstrated efficacy in enhancing psychological flexibility and self-management across various chronic diseases. When combined with parenting programmes, ACT has been effective in reducing parental anxiety and stress and ameliorating children's behavioural problems. Compared with education alone, our ACT-augmented parental training programme has shown greater effectiveness in improving parental psychological well-being and asthma management, resulting in decreased child asthma morbidity.[5] The present study aimed to investigate the effects and cost-effectiveness of an ACT-based asthma management programme, relative to treatment as usual (TAU), among children diagnosed with asthma and ADHD and their parents.

Methods

This assessor-blind, two-arm, repeated-measures, randomised controlled trial was conducted at a public hospital in Hong Kong between 1 April 2021 and 31 August 2023. Parents aged 18 to 65 years and their children aged 3 to 12 years with concurrent diagnoses of uncontrolled asthma (Childhood Asthma Control Test [C-ACT] score ≤19) and ADHD were invited to participate. Those involved in other intervention studies or displaying major comorbidities were excluded.

Participants were randomly allocated to either the ACT or TAU group in a 1:1 ratio, using permuted blocks of six to ensure balanced distribution. The TAU group received standard outpatient asthma care, which included biannual or quarterly paediatric follow-ups and medication reviews, along with regular asthma education sessions for parents every 3 to 4 weeks delivered by a paediatric respiratory nurse specialist. Referrals to community care and welfare services were made for parental training in ADHD management by psychiatrists or medical social workers. The ACT group received TAU plus a parenting programme titled Positive Parenting from Healthy Living, delivered in 2-hour sessions every 2 weeks, which aimed to improve parental self-regulation and positive parenting practices for childhood asthma management. Subsequently, 2-hour ACT sessions were introduced every 4 weeks for parents, focusing on enhancing parental psychological flexibility. These sessions included accepting parenting challenges, practising mindfulness, recognising the 'observer self', and committing to personal values while addressing parental well-being. The ACT module was customised for Hong Kong parents caring for children with asthma and ADHD; it emphasised coping with persistent thoughts related to comorbidities, managing emotions associated with asthma care and perceptions of ADHD, and navigating societal stigma related to ADHD. The costs associated with delivering the ACT programme were calculated.

The primary outcome was the frequency of unscheduled healthcare visits for childhood asthma exacerbations (including emergency department visits, specialist or private consultations, and hospitalisations) at 12 months post-intervention. Secondary outcomes were asthma symptoms assessed using the C-ACT, asthma-related behavioural issues assessed using the Asthma Behaviour Checklist, and ADHD symptoms assessed using the parent-reported Strengths and Weaknesses of ADHD-Symptoms and Normal-Behaviour Rating Scale (SWAN). For parents, psychological flexibility was assessed using the Acceptance and Action Questionnaire II (AAQ-II); higher scores indicated less flexibility. Parenting competence and self-efficacy in managing their child's asthma were measured using the Parenting Sense of Competency Scale and the Parent Asthma Management Self-Efficacy Scale. The Parent Experience of Child Illness (PECI) was used to assess parental adjustment to their child's illness, whereas the PedsQL Family Impact Module evaluated family and parental functioning. These outcomes were evaluated at 1 week, 6 months, and 12 months post-intervention.

Generalised estimating equations with a first-order autoregressive structure were used to assess intervention effects over time. Mediation analysis used structural equation modelling to examine whether early changes in parental psychological flexibility and competence mediated later parental and child outcomes. Cost-effectiveness analysis used retrospective cost data from post-intervention healthcare visits, considering both parental and societal perspectives; the incremental cost-effectiveness ratio was derived from differences in costs and healthcare visits between groups. All statistical analyses followed intention-to-treat principles, and the statistical significance threshold was set at $P<0.05$ (two-tailed).

Results

Of 5495 parent-child dyads screened, 130 were eligible; of these, 118 were randomly assigned to either the ACT (n=59) or TAU (n=59) group. Common reasons for non-participation were work or family commitments and concerns related to COVID-19. In the ACT group, 53 (89.8%) parents attended all sessions. Participation rates were 100% at baseline, 99.2% at 1 week, 94.1% at 6 months, and 89.0% at 12 months; retention rates were 89% at both 6 and 12 months.

Parental participants (mean age, 40.3 years) were predominantly mothers (91.5%) and housewives (54.2%) [Table 1]. Child participants (mean age, 7.9 years) had asthma onset at a mean age of 3.4 years and were mostly boys (73.7%). Of the child participants, 83.1% were receiving daily inhaled corticosteroids, 28.8% had experienced unscheduled healthcare visits for asthma in the previous year, 47.5% showed concomitant asthma and ADHD, and 26.2% were taking medication for ADHD. The two groups were comparable in baseline characteristics.

Over the 12-month follow-up period, children whose parents in the ACT group had significantly fewer unscheduled healthcare visits for asthma (adjusted incidence rate ratio [IRR]=0.33, $P<0.001$), fewer emergency department visits (adjusted IRR=0.25, $P=0.047$), and fewer consultations with private practitioners (adjusted IRR=0.34, $P=0.005$) [Table 2].

Significant time-by-group interactions were observed for asthma control (C-ACT score) and ADHD symptoms (SWAN total, inattention, and hyperactivity scores) [all $P<0.001$], with medium to large effect sizes (Cohen's d=0.76-1.43, all $P<0.001$-0.032). Asthma-related behavioural issues were also significantly reduced ($P<0.001$).

Among parents, there were significant improvements in psychological flexibility (AAQ-II score), parenting competence (PSOC total and subscale scores and PECI subscale scores), and self-efficacy concerning management of their child's

TABLE 1. Baseline characteristics of parents and children with asthma and attention-deficit hyperactivity disorder (ADHD).

Characteristic	All (n=118)*	Acceptance and commitment therapy group (n= 59)*	Treatment as usual group (n=59)*	P value
Relationship with the child				0.186
Father	10 (8.5)	3 (5.1)	7 (11.9)	
Mother	108 (91.5)	56 (94.9)	52 (88.1)	
Age, y	40.3±5.5	41.0±6.1	39.5±4.7	0.195
Educational attainment				0.663
Primary education or below	3 (2.5)	1 (1.7)	2 (3.4)	
Secondary education	76 (64.4)	42 (71.2)	34 (57.6)	
Tertiary education or above	39 (33.1)	16 (27.1)	23 (39.0)	
Monthly household income, HK$				0.575
Comprehensive Social Security Assistance	8 (6.8)	4 (6.8)	4 (6.8)	
<4000	1 (0.9)	1 (1.7)	0	
4000-9999	3 (2.5)	2 (3.4)	1 (1.7)	
10 000-24 999	39 (33.1)	21 (35.6)	18 (30.5)	
25 000-39 999	30 (25.4)	17 (28.8)	13 (22.0)	
40 000-59 999	24 (20.3)	8 (13.6)	16 (27.1)	
≥60 000	12 (10.2)	6 (10.2)	6 (10.2)	
Marital status				0.357
Single	4 (3.4)	3 (5.1)	1 (1.7)	
Married	103 (87.3)	49 (83.1)	54 (91.5)	
Separated, divorced, or widowed	11 (9.3)	7 (11.9)	4 (6.8)	
Occupation				0.567
Housewife	64 (54.2)	32 (54.2)	32 (54.2)	
Manager	4 (3.4)	0	4 (6.8)	
Professional	7 (5.9)	4 (6.8)	3 (5.1)	
Clerk	17 (14.4)	8 (13.6)	9 (15.3)	
Machine operator	2 (1.7)	1 (1.7)	1 (1.7)	
Service and sales	8 (6.8)	5 (8.5)	3 (5.1)	
Unemployed	1 (0.8)	1 (1.7)	0	
Part-time	15 (12.7)	8 (13.6)	7 (11.9)	
Sex of child				0.143
Male	87 (73.7)	40 (67.8)	47 (79.7)	
Female	31 (26.3)	19 (32.2)	12 (20.3)	
Age of child, y	7.9±2.2	8.0±2.1	7.8±2.3	0.653
Age at asthma onset, y	3.4±2.1	3.5±1.9	3.6±2.3	0.664
Age at ADHD onset, y	4.9±1.6	4.8±1.4	5.1±1.8	0.462
Current use of inhaled corticosteroids				0.703
None	20 (16.9)	12 (20.3)	8 (13.6)	
Beclomethasone dipropionate	70 (59.3)	35 (59.3)	35 (59.3)	
Fluticasone propionate	10 (8.5)	5 (8.5)	5 (8.5)	
Fluticasone propionate and salmeterol	11 (9.3)	5 (8.5)	6 (10.2)	
Budesonide	7 (5.9)	2 (3.4)	5 (8.5)	
ADHD diagnosis				0.306
Inattention	20 (16.9)	9 (15.3)	11 (18.6)	
Hyperactivity/impulsivity	42 (35.6)	25 (42.4)	17 (28.8)	
Combined	56 (47.5)	25 (42.4)	31 (52.5)	

* Data are presented as No. (%) of participants; missing data per variable is <3%.

TABLE 1. (cont'd)

Characteristic	All (n=118)*	Acceptance and commitment therapy group (n= 59)*	Treatment as usual group (n=59)*	P value
Current use of ADHD medications				0.593
None	87 (73.7)	41 (69.5)	46 (78.0)	
Yes, central nervous system stimulants	26 (22.0)	15 (25.4)	11 (18.6)	
Yes, non-central nervous system stimulants	1 (0.8)	1 (1.7)	0	
Yes, both	4 (3.4)	2 (3.4)	2 (3.4)	
Specialist outpatient visits due to asthma exacerbations over the past 12 months				0.580
None	106 (89.8)	53 (89.8)	53 (89.8)	
1-2	11 (9.3)	6 (10.2)	5 (8.5)	
3-4	1 (0.8)	0	1 (1.7)	
Private practitioner clinic visits due to asthma exacerbations over the past 12 months				0.115
None	101 (85.6)	46 (78.0)	55 (93.2)	
1-2	11 (9.3)	9 (15.3)	2 (3.4)	
3-4	3 (2.5)	2 (3.4)	1 (1.7)	
≥5	3 (2.5)	2 (3.4)	1 (1.7)	
Emergency department visits due to asthma exacerbations over the past 12 months				0.648
None	113 (95.8)	56 (94.9)	57 (96.6)	
1-2	5 (4.2)	3 (5.1)	2 (3.4)	
Hospitalisation due to asthma exacerbations over the past 12 months				0.098
None	107 (90.7)	52 (88.1)	55 (93.2)	
1-2	7 (5.9)	6 (10.2)	1 (1.7)	
3-4	4 (3.4)	1 (1.7)	3 (5.1)	
Unscheduled healthcare service use due to asthma exacerbations over the past 12 months				0.204
None	84 (71.2)	37 (62.7)	47 (79.7)	
1-2	22 (18.6)	15 (25.4)	7 (11.9)	
3-4	8 (6.8)	5 (8.5)	3 (5.1)	
≥5	4 (3.4)	2 (3.4)	2 (3.4)	

asthma (Parent Asthma Management Self-Efficacy subscale score). These improvements showed significant time-by-group interactions (all P<0.001) and medium to large effect sizes (Cohen's d=0.65-1.59, all P<0.001-0.032). Improvements in family functioning (Family Impact Module subscale score) also were significant (all P<0.001).

Changes in AAQ-II and PSOC scores at 1-week post-intervention significantly mediated improvements in C-ACT scores, Parent Asthma Management Self-Efficacy subscale scores, and the PECI long-term uncertainty subscores at 6 months post-intervention (P=0.001-0.034). Changes in AAQ-II and/or PSOC total scores at 6 months post-intervention significantly mediated improvements in SWAN total and hyperactivity scores, as well as PECI long-term uncertainty and emotional resources subscale scores, at 12 months (Fig).

By the 12-month follow-up, parents in the ACT group incurred out-of-pocket costs totalling HK$7750 for 26 unscheduled asthma-related visits, whereas parents in the TAU group paid HK$20 210 for 69 visits. Compared with baseline, the ACT group avoided 38 visits, whereas the TAU group experienced 22 additional visits. The incremental cost-effectiveness ratio was HK$913 per visit avoided (HK$54 770 incremental cost divided by the 60 visits avoided).

TABLE 2. Medical consultations due to asthma exacerbations over the past 12 months in the acceptance and commitment therapy (ACT) group and the treatment as usual (TAU) group across time.

Outcome	Baseline*	1 week*	6 months*	12 months*	P value			Adjusted incidence rate ratio (95% confidence interval)	P value
					Time effect	Group effect	Time-by-group effect		
Emergency department visits					0.445	0.934	0.042	0.25 (0.06-0.93)	0.047
ACT group	0.12±0.06	0.12±0.05	0.04±0.03	0.04±0.03					
TAU group	0.04±0.02	0.15±0.10	0.25±0.11	0.28±0.11					
Specialist outpatient visits					0.634	0.020	0.686	0.43 (0.17-1.10)	0.077
ACT group	0.24±0.11	0.18±0.07	0.09±0.05	0.12±0.05					
TAU group	0.36±0.12	0.37±0.12	0.29±0.11	0.26±0.07					
Private practitioner clinic visits					0.499	0.194	0.098	0.34 (0.16-0.74)	0.005
ACT group	0.58±0.20	0.51±0.17	0.38±0.09	0.31±0.08					
TAU group	0.36±0.13	0.44±0.14	0.58±0.19	0.68±0.21					
Hospital admissions					0.076	0.786	0.224	0.63 (0.12-3.22)	0.580
ACT group	0.17±0.07	0.10±0.05	0.04±0.03	0.04±0.03					
TAU group	0.17±0.07	0.03±0.02	0.10±0.04	0.08±0.04					
Total number of unscheduled healthcare service visits					0.922	0.067	0.001	0.33 (0.19-0.55)	<0.001
ACT group	0.98±0.24	0.90±0.20	0.54±0.10	0.50±0.10					
TAU group	0.63±0.80	0.98±0.27	1.20±0.33	1.30±0.32					
Total number of days of inpatient hospital stay					-	-	-	-	-
ACT group	4.00±0.62	4.00±1.73	4.50±0.71	4.00±0.01					
TAU group	4.75±0.63	4.00±1.41	3.80±0.84	4.25±0.25					

* Data are presented as mean ± standard error.

Discussion

Our findings demonstrated the efficacy of the ACT intervention for parents. Significant outcomes included reduced childhood asthma morbidity and ADHD symptoms, as well as decreased parental psychological distress. Improvements in parenting competence and asthma management self-efficacy persisted at 12 months. Children whose parents had received the ACT intervention displayed a significant reduction in emergency department visits and unscheduled healthcare utilisation for asthma exacerbations at the 12-month follow-up.

The ACT intervention directly affected parental psychological flexibility and parenting competence, whereas its mediating effect on health outcomes was more nuanced. Partial mediation was observed at 6 months for illness management uncertainty and asthma control; significant indirect effects for ADHD symptoms and parental perceptions of uncertainty and emotional resources were observed at 12 months. These findings suggest that the intervention is particularly effective over time, although other factors may moderate outcomes and thus warrant further investigation.

Our study's high recruitment and retention rates underscore the programme's feasibility and acceptability, highlighting gaps in current healthcare systems for families with comorbid conditions. Economic benefits were also observed: healthcare costs for the ACT group were reduced at 12 months post-intervention.

Limitations of the study include potential confounding factors, timing during the post-pandemic period, and limited generalisability due to the single-centre design and predominant participation of mothers. The use of parental reports to evaluate ADHD symptoms also indicates the need for a more robust multi-informant approach in future studies.

Our findings support the inclusion of ACT and positive parenting strategies in healthcare professional training and care guidelines. Future studies should aim to compare the specific benefits of ACT with those of other active treatments and ensure that interventions are precisely tailored to family needs.

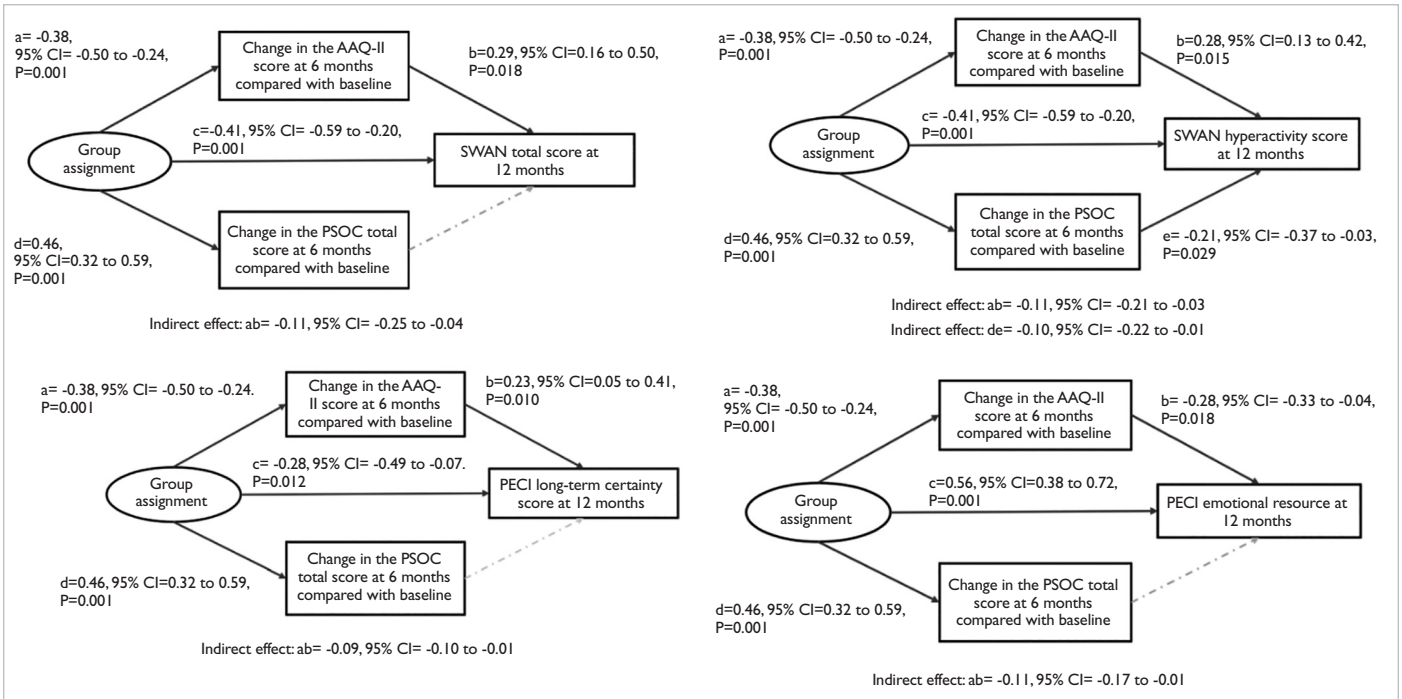

FIG. Significant indirect effects of acceptance and commitment therapy at 1-week post-intervention on scores of the Acceptance and Action Questionnaire-II (AAQ-II) and the Parenting Sense of Competence Scale (PSOC), mediating scores of the Parent Experience of Child Illness (PECI) and the Strengths and Weaknesses of ADHD-Symptoms and Normal Behaviours Rating Scale (SWAN) at 6-month post-intervention.
Abbreviation: 95% CI = 95% confidence interval.

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Disclosure

The results of this research have been previously published in:

1. Chong YY, Chien WT, Fung KP, Leung SP, Lam SY. Acceptance and commitment therapy–based parenting program in children with co-occurring asthma and ADHD: a randomized clinical trial. JAMA Pediatr 2025;179:846-56.
2. Chong YY, Yau PT, Kwan JYM, Chien WT. Roles of psychological flexibility, parenting competence, and asthma management self-efficacy in the functioning outcomes of parents of children with asthma co-occurring with attention-deficit/hyperactivity disorder. Eur J Investig Health Psychol Educ 2024;14:2835-49.

References

1. Cortese S, Sun S, Zhang J, et al. Association between attention deficit hyperactivity disorder and asthma: a systematic review and meta-analysis and a Swedish population-based study. Lancet Psychiatry 2018;5:717-26.
2. Wong GW, Leung TF, Ko FW. Changing prevalence of allergic diseases in the Asia-pacific region. Allergy Asthma Immunol Res 2013;5:251-7.
3. Liu A, Xu Y, Yan Q, Tong L. The prevalence of attention deficit/hyperactivity disorder among Chinese children and adolescents. Sci Rep 2018;8:11169.
4. Eccleston C, Fisher E, Law E, Bartlett J, Palermo TM. Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database Syst Rev 2015;4:CD009660.
5. Chong YY, Mak YW, Leung SP, Lam SY, Loke AY. Acceptance and commitment therapy for parental management of childhood asthma: an RCT. Pediatrics 2019;143:e20181723.

Music therapy for social skills in children with autism spectrum disorder and intellectual disability: abridged secondary publication

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KEY MESSAGES

1. Group music therapy was effective in decreasing autistic features and negative behaviours among children with autism spectrum disorder and intellectual disability, comparable to non-musical behavioural interventions.
2. Children who received music therapy were more engaged and made more initiations, compared with those who received non-musical behavioural interventions, although there was no significant difference between groups concerning changes in autistic features.
3. Children with positive neural responses to social scenes showed increased initiation behaviour during both interventions, whereas children with positive neural responses to music showed increased initiation behaviour during music therapy alone.
4. Children's social or musical affinity may affect outcomes. Neural markers may help match children with the appropriate intervention.
5. Children did not generalise the learned social skills to other settings. Future research may aim to increase skill transfer by assigning home practice.

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Introduction

Autism spectrum disorder (ASD) is characterised by difficulties in social communication and interaction, as well as restricted and repetitive behaviours, interests, and activities. The incidence of ASD worldwide is approximately 1 in 100 individuals; it co-occurs with intellectual disability (ID) in an average of 33% of cases.[1] Behavioural interventions targeting social skills remain the core strategy to support the integration of these children into school and society.

Music therapy aids therapists in developing relationships with individuals with ASD and helps them achieve individualised goals, according to the National Clearinghouse of Autism Evidence and Practice. A meta-analysis showed that music therapy can improve autistic children's social responses but not adaptive behaviour or speech.[2] Group music therapy enables participants to practise their social skills with peers while reducing instructor and venue costs.[3] It is thus more viable for families and schools. Identifying markers of intervention effectiveness can also lower costs. Children with higher social inclinations may show better intervention outcomes, and those who prefer music may make greater improvements. Neural responses to social or musical stimuli may serve as candidate neural markers.

This study aimed to examine whether music therapy provides additional benefits over non-musical behavioural interventions among children with ASD and ID in Hong Kong, and whether children's neural responses to social and musical stimuli prior to intervention predict effectiveness.

Methods

Children aged 6 to 13 years with ASD and ID who had no severe physical or sensory disabilities, no other neurodevelopmental, psychiatric, or neurological comorbidities, and were not taking any psychiatric medication were recruited through advertisements in special schools. Participants were randomly assigned to receive either music therapy by certified music therapists or a non-musical social skills intervention by trainers with experience in leading interventions for children with special needs. Each music therapy session followed a standard structure, including a hello song, musical activities, and a goodbye song. In the control group, each session followed a similar structure, consisting of opening greetings, theme-based social activities, and a closing activity. The activities and games varied during each session and were integrated in later sessions to revisit and practise social skills. Participants received one 45-minute session of social skills training per week for 12 weeks. In total, 10 groups of six to eight children were established between June 2021 and September 2022.

Participants were assessed 2 weeks before the intervention and at 2 weeks and 4 months after the intervention. The 15-item Childhood Autism Rating Scale was used to assess autistic features (eg, verbal abilities, eye contact). The cut-off score for ASD was 30; higher scores indicated more autistic features. The 65-item, parent-rated Social Responsiveness Scale was used to assess children's general social skills (eg, difficulty maintaining a conversation). The cut-off score for ASD was 60; higher scores indicated greater social impairment.

Children's social behaviours during the sessions were assessed based on the number of seconds observed during 10 minutes of video recording, including negative behaviours (eg, speaking or acting out of turn), engaged behaviours (eg, responding to requests), and initiations (eg, starting social exchanges or asking questions).

Brainwave data were collected using headsets with 14 electrodes. Participants silently engaged in three 5-minute tasks: viewing social scenes, viewing moving shapes, or listening to preferred music. Frontal alpha asymmetry (FAA), a neural response sensitive to emotions and motivation in both clinical and typical populations, was measured. A left-lateralised FAA suggests an approach state, whereas a right-lateralised FAA suggests an avoidance state.[4] Neural measurements reflect automatic responses to stimuli and may supplement children's self-report data, thus avoiding verbal prompts for children who may find words challenging to comprehend or express. The FAA indices were calculated by subtracting neural responses to the control condition of viewing moving shapes from neural responses to social scenes or preferred music.

TABLE 1. Characteristics of participants.

Characteristic	Overall (n=77)*	Music therapy (n=37)*	Control (n=40)*	P value
Child age, y	8.71±2.03	8.32±1.86	9.08±2.13	0.13
Child sex				0.58
Male	67 (87.0)	32 (86.5)	35 (87.5)	
Female	10 (13.0)	5 (13.5)	5 (12.5)	
Parents' marital status				0.06
Never married	2 (2.6)	1 (2.7)	1 (2.5)	
Widowed	3 (3.9)	0	3 (7.5)	
Divorced	5 (6.5)	1 (2.7)	4 (10.0)	
Married	67 (87.0)	35 (94.6)	32 (80.0)	
Paternal education				0.97
Primary school or below	2 (2.6)	0	2 (5.0)	
Secondary school	44 (57.1)	25 (67.6)	19 (47.5)	
College and university	21 (27.3)	7 (18.9)	14 (35.0)	
Master's degree or above	6 (7.8)	4 (10.8)	2 (5.0)	
Unknown	4 (5.2)	1 (2.7)	3 (7.5)	
Maternal education				0.11
Primary school or below	2 (2.6)	1 (2.7)	1 (2.5)	
Secondary school	44 (57.1)	18 (48.6)	26 (65.0)	
College and university	25 (32.5)	13 (35.1)	12 (30.0)	
Master's degree or above	6 (7.8)	5 (13.5)	1 (2.5)	
Household monthly income, HK$				0.83
≤10 000	8 (10.4)	3 (8.1)	5 (12.5)	
10 001-20 000	18 (23.4)	8 (21.6)	10 (25.0)	
20 001-30 000	21 (27.3)	14 (37.8)	7 (17.5)	
30 001-40 000	10 (13.0)	5 (13.5)	5 (12.5)	
40 001-50 000	8 (10.4)	2 (5.4)	6 (15.0)	
50 001-60 000	3 (3.9)	0	3 (7.5)	
≥60 001	9 (11.7)	5 (13.5)	4 (10.0)	
No. of siblings				0.81
0	26 (33.8)	10 (27.0)	16 (40.0)	
1	40 (51.9)	24 (64.9)	16 (40.0)	
2	9 (11.7)	3 (8.1)	6 (15.0)	
≥3	2 (2.6)	0	2 (5.0)	

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

Results

Of 255 children screened, 77 participated and were included in the analysis; of these, 10 withdrew and 67 (33 in the music therapy group and 34 in the non-musical social skills intervention group) were available at the 4-month follow-up. The two groups were comparable in terms of baseline characteristics (Table 1).

After the intervention, children in both groups showed significant improvement in Childhood Autism Rating Scale scores for autistic features, although parent-rated Social Responsiveness Scale scores for children's social skills did not significantly differ between or within groups (Table 2). Children in both groups showed significantly decreased negative behaviours. Children in the music therapy group showed increased engagement and initiation behaviours, whereas children in the control group showed decreased engagement behaviours. Children with enhanced FAA responses to social scenes showed greater improvement in initiation behaviour during both interventions; children with enhanced FAA responses to music showed increased negative and initiation behaviours but decreased engagement behaviour during music therapy alone, perhaps due to over-eagerness.

Discussion

Children in both the music therapy group and the non-musical social skills intervention group displayed better prosocial behaviours after the

intervention, consistent with a previous report that children attending music therapy showed increases in engagement and initiation behaviours, suggesting that musical exchanges can serve as a conduit for learning appropriate social behaviours.[3]

Children's pre-intervention neural data (reflecting social or musical affinity) could predict improvements in initiation behaviour. Neural indices may help match children with the appropriate intervention for more personalised care.

However, parents did not report significant improvement in their children's social skills after the intervention, consistent with the results of a large-scale randomised controlled trial.[2] This finding may be attributable to the nature of the parent-child relationship, which is resistant to change in social interaction patterns, and to the study period coinciding with the COVID-19 pandemic. Home practice and family-based music therapy warrant further study because they may alleviate caregiver stress and improve family relationships while improving children's social skills.

TABLE 2. Comparison of Childhood Autism Rating Scale (CARS-2) scores, Social Responsiveness Scale (SRS-2) scores, and observed social behaviours between groups.

Variable	Music therapy (n=33)	Control (n=34)	P value
2 weeks before intervention			
SRS-2	77.5±7.3	77.3±6.4	0.910
CARS-2	32.1±4.2	31.6±5.3	0.651
2 weeks after intervention			
SRS-2	77.0±8.1	78.0±6.2	0.581
CARS-2	30.8±4.8	29.9±4.8	0.469
4 months after intervention			
SRS-2	78.7±7.1	77.3±7.0	0.409
CARS-2	30.7±3.3	29.8±4.2	0.321
Beginning of intervention			
Negative behaviour, s	42.5±57.1	49.4±81.0	0.687
Engagement, s	146±72.5	107±48.6	0.011
Initiation, s	7.6±9.7	12.9±30.2	0.332
End of intervention			
Negative behaviour, s	29.0±34.4	28.5±44.8	0.957
Engagement, s	165±101	86.6±59.6	<0.001
Initiation, s	12.4±19.4	11.4±14.3	0.808

* Data are presented as mean ± standard deviation.

Conclusion

Music therapy, as an allied health profession, is a viable behavioural intervention for children with ASD and ID.

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Disclosure

The results of this research have been previously published in:

1. Yum YN, Lau WK, Poon K, Ho FC. Music therapy as social skill intervention for children with comorbid ASD and ID: study protocol for a randomized controlled trial. BMC Pediatr 2020;20:545.
2. Yum YN, Poon K, Lau WK, et al. Music therapy improves engagement and initiation for autistic children with mild intellectual disabilities: a randomized controlled study. Autism Res 2024;17:2702-22.

References

1. Zeidan J, Fombonne E, Scorah J, et al. Global prevalence of autism: a systematic review update. Autism Res 2022;15:778-90.
2. Ke X, Song W, Yang M, Li J, Liu W. Effectiveness of music therapy in children with autism spectrum disorder: a systematic review and meta-analysis. Front Psychiatry 2022;13:905113.
3. LaGasse AB. Effects of a music therapy group intervention on enhancing social skills in children with autism. J Music Ther 2014;51:250-75.
4. Lauttia J, Helminen TM, Leppänen JM, et al. Atypical pattern of frontal EEG asymmetry for direct gaze in young children with autism spectrum disorder. J Autism Dev Disord 2019;49:3592-601.

Epstein-Barr virus–specific T cell and NK cell responses in paediatric patients with infectious mononucleosis or post-transplant lymphoproliferative disorder: abridged secondary publication

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KEY MESSAGES

1. In patients with post-transplant lymphoproliferative disorder (PTLD), Epstein-Barr virus (EBV)-specific $CD8^+$ polyfunctional T cells were limited at 24 months after diagnosis, despite clinical remission.
2. In patients with PTLD, the frequency of potent degranulating $CD56^{dim}NKG2A^+KIR^-$ NK cells diminished from diagnosis to clinical remission.
3. In patients with PTLD, plasma EBV viral loads were weakly correlated with blood tacrolimus levels. Prolonged immunosuppression may result in suboptimal immune control of EBV.

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Introduction

Post-transplant lymphoproliferative disorder (PTLD) is a rare but potentially life-threatening complication, frequently associated with Epstein-Barr virus (EBV) among transplant recipients who receive immunosuppressants to suppress T-cell function. Natural killer (NK) cells have an important role in controlling viral infection. This study aimed to explore the roles of distinct NK cell subsets and EBV-specific T cells in the control of EBV infection among patients with infectious mononucleosis (IM) or PTLD who were receiving tacrolimus. The effects of tacrolimus on the development of T and NK cells and the control of EBV loads were also determined.

Methods

We recruited 20 children with IM and 15 children with PTLD. Diagnosis of IM was based on clinical symptoms (including fever, cervical lymphadenopathy, pharyngitis, and hepatosplenomegaly) and the serological pattern of primary EBV infection. Diagnosis of PTLD was based on histological features of biopsy tissues (n=14) or positron emission tomography–computed tomography findings (n=1).

Peripheral blood mononuclear cells (PBMCs) were isolated from heparinised blood. Development of T and NK cells was determined by flow cytometric analysis. NK cell functions were assessed through expression of the proliferation marker Ki67 and via co-culture of PBMCs with the cell lines LCL721.221 or K562. EBV copy numbers in plasma and PBMCs were quantified. Correlations between EBV copy numbers and tacrolimus levels were determined using a two-tailed Spearman test.

Results and discussion

We assessed the development of EBV-specific polyfunctional T cell (PFC) and NK cell subsets. In patients with IM or PTLD, EBV-specific $CD4^+$ and $CD8^+$ T cells were identified at diagnosis and at post-diagnosis time points after EBV peptide stimulation. Among patients with PTLD, frequencies of BMLF1-specific $CD8^+$ T cells significantly increased at 24 months after diagnosis, and an increasing trend of EBV-specific $CD8^+$ T cells over time was observed, suggesting restoration of T-cell function after recovery. Among patients with IM, we observed a decreasing trend of EBV lytic antigen BMLF1- and BZLF1-specific $CD4^+$ PFCs but an increasing trend of EBV latent antigen EBNA1-specific $CD4^+$ PFCs at 12 months after diagnosis. Among patients with PTLD, a significant decrease in EBV lytic antigen BZLF1-specific $CD4^+$ PFCs was identified at 24 months after diagnosis. Among patients with IM—but not those with PTLD—we observed a decreasing trend in the frequency of EBV lytic antigen BMLF1-specific $CD8^+$ PFCs but an increasing trend of EBV latent antigen EBNA1- and EBNA3A-specific $CD4^+$ PFCs at 12 months after diagnosis. Additionally, the frequencies of all EBV lytic and latent antigen-specific $CD8^+$ PFCs remained low at 24 months after

diagnosis. Among patients with IM, $CD4^+$ and $CD8^+$ PFCs showed an increase in functionality over time. However, among patients with PTLD, EBNA3A-specific $CD8^+$ PFCs were only able to gain two additional combinations of function after recovery. This lack of polyfunctional EBV-specific $CD4^+$ and $CD8^+$ T cells suggested impairment of T-cell function due to long-term immunosuppressive drug therapy.

We assessed the frequencies of different NK cell subsets from diagnosis to 12 or 24 months. Most patients with IM or PTLD showed >90% $CD56^{dim}$ NK cells within their $CD3^-CD56^+$ NK cell population in peripheral blood. We dissected the distinct NK cell subsets within $CD56^{dim}$ NK cells. Among patients with IM, $NKG2A^+KIR^-$ NK cells constituted the majority of $CD56^{dim}$ NK cells, whereas among patients with PTLD, $NKG2A^-KIR^+$ NK cells were predominant. Longitudinal analysis of subset frequencies showed significant differences between the two cohorts. In patients with PTLD, the low frequencies of $NKG2A^+KIR^-$ NK cells were not related to treatment, and the difference in frequency of the $CD56^{dim}NKG2A^+KIR^-$ NK cell subset suggested suboptimal development of NK cells.

We found significantly higher frequencies of Ki67-expressing $CD56^{dim}NKG2A^+KIR^-$ NK cells in patients with IM than in patients with PTLD from diagnosis to 3 months after diagnosis. In contrast, the level of Ki67-expressing cells among $CD56^{dim}NKG2A^-KIR^+$ NK cells did not significantly differ between the two cohorts, nor did it change over time. A prior study demonstrated the importance of the $CD56^{dim}NKG2A^+KIR^-$ subset in the immune control of EBV.[1] The $CD56^{dim}NKG2A^+KIR^-$ NK cell subset showed more degranulation than $CD56^{dim}NKG2A^-KIR^+$ NK cell subset. Interestingly, patients with IM or PTLD showed similar degranulation levels of the $CD56^{dim}NKG2A^+KIR^-$ NK cell subset in response to LCL721.221. In patients with PTLD, the $CD56^{dim}NKG2A^+KIR^-$ NK cell subset could degranulate efficiently upon stimulation with EBV-infected B cells. The diminished frequency of potent degranulating $CD56^{dim}NKG2A^-KIR^+$ NK cells might lead to suboptimal immune control.

Plasma and PBMC EBV viral levels were significantly higher in patients with PTLD than in patients with IM at diagnosis and at 12 months post-diagnosis (data not shown). Despite a significant decrease in plasma viral loads over time, some patients with PTLD (n=4) showed persistently elevated EBV viral loads up to 24 months. All patients with PTLD showed persistently elevated EBV viral loads in their PBMCs up to 24 months (data not shown). We assessed the kinetics of plasma EBV viral loads and trough blood tacrolimus levels in 15 patients with PTLD from diagnosis onwards. Patients with increased blood tacrolimus levels had increased plasma EBV viral loads (data not shown). Consistent with these findings, plasma EBV viral loads showed a weak correlation with blood tacrolimus levels (r=0.1620, P=0.0191). Prolonged immunosuppression might play a role in suboptimal immune control of EBV, as indicated by persistent EBV viraemia and impaired T- and NK-cell development in patients with PTLD.

The new knowledge generated by this research study can be used to design specific immune assays that complement measurement of EBV loads in the management of PTLD. The findings also may lead to the development of a clinical algorithm to guide reduction of immunosuppression or pre-emptive treatment of PTLD.

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Disclosure

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1. Lam JKP, Azzi T, Hui KF, et al. Co-infection of cytomegalovirus and Epstein-Barr virus diminishes the frequency of $CD56^{dim}NKG2A^+KIR^-$ NK Cells and contributes to suboptimal control of EBV in immunosuppressed children with post-transplant lymphoproliferative disorder. Front Immunol 2020;11:1231.

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