SUPPLEMENT 3

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Health and Medical Research Fund

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HONG KONG MEDICAL JOURNAL 香港醫學雜誌
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SUPPLEMENT 3

Health and Medical Research Fund

Research Dissemination Reports

CHILDREN'S 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 11 dissemination reports of projects related to traditional Chinese medicine, health promotion, infectious diseases, non-communicable diseases, and children's health. In particular, research findings of three projects may provide insights to enhance clinical practices and help inform health policy formulation in Hong Kong.

Anti-psychotic therapy for schizophrenia spectrum disorders (SSD) may induce metabolic syndrome. Berberine, a natural plant alkaloid derived from traditional Chinese herbal medicine, has been found to have weight loss, anti-diabetic, and anti-hyperlipidaemic properties. Chan et al[1] conducted a randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of adjunctive berberine in controlling weight gain and improving other metabolic variables among 113 patients with SSD who had developed metabolic syndrome. They found that compared with placebo, berberine treatment led to substantial reductions in body weight, body mass index, diastolic blood pressure, total cholesterol, low-density lipoprotein, fasting glucose, and glycated haemoglobin at 6 weeks and 12 weeks post-treatment. They concluded that berberine, as an adjuvant, was safe and effective in reducing anti-psychotic-associated weight gain and improving metabolic syndrome without exacerbating psychotic symptoms or inducing other adverse effects.

Human papilloma virus (HPV) can cause genital warts and penile/ anal cancer in men. Men who have sex with men (MSM) are at higher risk of contracting HPV and related diseases. HPV vaccination is very effective in preventing genital warts and cancer in MSM; however, vaccine uptake is very low among MSM in Hong Kong. Wang et al[2] evaluated the efficacy of two online theory-based interventions with and without motivational interviewing via phone in increasing the rate of complete (three-dose) HPV vaccination among 624 Hong Kong Chinese MSM. They found that 75 participants received a full course of HPV vaccination during 24-month period following the intervention. HPV vaccine uptake was significantly higher among the group receiving health communication plus motivational interviewing compared with the control group. Health communication alone was somewhat effective in increasing HPV vaccination compared with control, but the increase did not reach statistical significance. The intervention has been integrated into existing human immunodeficiency (HIV) testing and counselling services implemented by a non-governmental organisation focused on HIV prevention in Hong Kong.

Lupus nephritis is a serious manifestation of systemic lupus erythematosus; long-term monitoring to predict and prevent clinical relapses is challenging. Changes in B-cell-related cytokines may offer a convenient biomarker for monitoring asymptomatic serological reactivation (ASR). Yap et al[3] conducted a randomised controlled trial of pre-emptive immunosuppressive treatment (tapered doses of prednisolone and/or azathioprine/mycophenolate mofetil) among 43 patients with lupus nephritis experiencing ASR. They found that pre-emptive increase in immunosuppression could reduce renal relapse among participants and was well-tolerated. B-cell signatures, especially B lymphocyte activation factor, may serve as biomarkers for treatment-response monitoring.

Supplement editors

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2. Wang Z, Lau JTF, Lam PPK, Chan P, Fong F, Mo PKH. Promotion of human papillomavirus vaccination among Chinese men who have sex with men: abridged secondary publication. Hong Kong Med J 2023;29(Suppl 3):S9-15.
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Berberine for antipsychotic-induced metabolic syndrome in patients with schizophrenia spectrum disorders: abridged secondary publication

MY Chan, SC Man, M Lam, WH Lai, ZS Qin, MKR Ng, CK Lee, YHE Chen, HME Lee, LY Liu, HK Wong, ZJ Zhang *

KEY MESSAGES

1. Antipsychotic therapy for schizophrenia spectrum disorders may induce metabolic syndrome.
2. Compared with placebo, berberine adjunctive treatment led to substantial reductions in body weight, body mass index, diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, and glycated haemoglobin at 6 weeks, 12 weeks, or both (all $P<0.05$). The severity of psychotic and movement symptoms did not change in either group during the course of treatment. No serious adverse events were reported.
3. As an adjuvant, berberine is safe and effective in terms of reducing antipsychotic-associated weight gain and improving metabolic syndrome, without exacerbating psychotic symptoms or inducing other adverse effects.

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HMRF project number: 14151891

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Introduction

Antipsychotic therapy for schizophrenia spectrum disorders (SSDs) may lead to various adverse drug reactions.[1] Metabolic syndrome (MetS) is associated with the use of atypical antipsychotics; its prevalence is 33.4% in patients with severe mental illness.[2] Berberine is a natural plant alkaloid isolated from the Chinese herbal medicine *Coptis chinensis*; it has weight-lowering, antidiabetic, and anti-hyperlipidaemic effects.[3] This study aimed to evaluate the efficacy and safety of berberine adjunctive treatment in terms of controlling weight gain and improving other anthropometric and metabolic variables in patients with SSDs who had MetS.

Methods

This randomised, double-blind, placebo-controlled trial was conducted between April 2018 and December 2020 at Queen Mary Hospital, Kowloon Hospital, Castle Peak Hospital, and The University of Hong Kong. Patients were invited to participate if they were aged 18 to 65 years with a primary diagnosis of SSD (based on the Classification of Mental and Behavioural Disorders, 10th version), had been receiving atypical antipsychotic treatment for ≥3 months, had a stable condition, and had developed MetS (based on the International Diabetes Federation criteria[4]). Patients were excluded if they had serious comorbid gastrointestinal or other unstable medical conditions, a history of suicidal attempts, any alcohol abuse or drug abuse in the past 3 months, and/or any investigational drug treatment in the past 6 months; patients were also excluded if they were pregnant or breastfeeding.

Participants were randomly assigned (at a 1:1 ratio) to the placebo or berberine group. All study medication was prepared in identical packaging and labelled with only a code. Participants continued their current atypical antipsychotic treatment as prescribed by their psychiatrist. Concomitant use of other psychotropic drugs (eg, antidepressants, anxiolytics, mood stabilisers, hypnotics, and anticholinergics) was allowed as usual, as was concomitant use of anti-hyperlipidaemic, antihypertensive, and antidiabetic treatment if the type and dosage of medication remained stable throughout the study.

Participants received additional treatment with either berberine or placebo tablets (0.3 g, twice daily before meals in the morning and evening) for 12 consecutive weeks. For participants taking psychotropic or other medications, an interval of at

least 2 hours was recommended between berberine/placebo intake and the use of other medications.

Berberine and placebo tablets were manufactured by Wah Kin Pharmaceutical Products Company, which registered the berberine tablets as over-the-counter drugs in Hong Kong. Berberine tablets were manufactured as yellow sugar-coated tablets, each containing 100 mg of berberine hydrochloride. Placebo tablets were manufactured with taste, appearance, and size identical to berberine tablets.

The primary outcome was the change in body weight from baseline to each time point. Secondary outcome measures were body mass index (BMI), waist circumference (WC), blood pressure, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, fasting blood glucose (FBG), and glycated haemoglobin (HbA1c). The severity of psychotic symptoms, antipsychotic-induced movement symptoms, and adverse effects associated with therapy were also evaluated.

The intention-to-treat approach was used. A linear mixed-effects model was used to compare changes from baseline in terms of WC, BMI, blood pressure, biochemical variables, and scores on the Positive and Negative Syndrome Scale and its subscales. The model was established using time and group as categorical fixed factors and random intercepts within a scaled identity covariance matrix. Baseline LDL cholesterol was regarded as a covariate in the analysis of anthropometric variables (net weight gain, WC, and BMI). Respective baseline variables were regarded as covariates in analyses of blood pressure and metabolic variables. The Wilcoxon rank-sum test was used to assess differences in Extrapyramidal Symptom Rating Scale–Abbreviated scores. Student's *t* test was used to assess differences in continuous baseline variables between the two groups. Categorical baseline variables and adverse event incidences were analysed using the Chi squared test or Fisher's exact test. Statistical significance was defined as a two-tailed P value of <0.05.

Results

Of 286 patients screened, 113 agreed to participate and were randomly assigned to the berberine (n=58) and placebo (n=55) groups; 25 participants (17 in the berberine group and 8 in the placebo group) did not complete the 3-month study. The two groups were comparable in terms of all baseline variables, except for LDL cholesterol (Table 1).

Compared with the placebo group, the berberine group displayed significant decreases in body weight at 9 weeks (-0.47 vs 0.28 kg, P=0.031) and 12 weeks (-0.71 vs 0.37 kg, P=0.002). The placebo group displayed a slight increase in body weight (0.22 kg) at 12 weeks (Table 2). The berberine group displayed significant reductions in BMI (P=0.012), WC (P=0.034), and HbA1c (P=0.001) at 12 weeks; in triglycerides (P=0.038 and P=0.021), total cholesterol (both P<0.0001), and LDL cholesterol (both P<0.0001) at both 6 and 12 weeks; and in HDL cholesterol (P=0.001) and FBG (P=0.009) at 6 weeks. Compared with the placebo group, the berberine

TABLE 1. Baseline characteristics of participants

Variables	Berberine (n=58)*	Placebo (n=55)*	P value
Age, y	39.3±11.3	36.2±10.8	0.138
Sex			0.954
Male	25 (43.1)	24 (43.6)	
Female	33 (56.9)	31 (56.4)	
Marital status			0.389
Single/divorced/widowed	39 (67.2)	38 (69.1)	
Married	19 (32.8)	17 (30.9)	
Occupation			0.276
Professional or associate professional	24 (41.4)	19 (34.6)	
Skilled or non-skilled worker	14 (24.1)	18 (32.7)	
Others	20 (34.5)	18 (32.7)	
Antipsychotic regimen			0.997
Monotherapy	39 (67.2)	37 (67.3)	
Combination therapy	19 (32.8)	18 (32.7)	
Type of schizophrenia spectrum disorder			0.754
Schizophrenia	47 (81.0)	40 (72.7)	
Schizoaffective disorder	4 (6.9)	5 (9.1)	
Unspecific non-organic psychosis	6 (10.3)	9 (16.4)	
Persistent delusional disorder	1 (1.7)	1 (1.8)	
Duration of schizophrenia spectrum disorder, mo	138.4±113.9	120.3±107.2	0.386
Weight, kg	81.6±14.3	79.2±13.7	0.375
Waist circumference, cm	101.1±10.6	98.6±9.6	0.204
Body mass index, kg/m^2	29.3±4.5	29.2±4.2	0.827
Systolic blood pressure, mmHg	126.5±17.6	123.2±15.4	0.293
Diastolic blood pressure, mmHg	79.5±11.1	75.5±10.2	0.053
Triglycerides, mmol/L	2.3±1.4	2.2±2.1	0.873
Total cholesterol, mmol/L	5.4±1.1	5.0±1.2	0.072
High-density lipoprotein cholesterol, mmol/L	1.2±0.3	1.4±0.8	0.101
Low-density lipoprotein cholesterol, mmol/L	3.4±1.0	2.9±0.9	0.004
Fasting blood glucose, mmol/L	6.0±2.2	5.5±1.2	0.144
Glycated haemoglobin, %	6.1±1.3	5.8±0.7	0.170
Positive and Negative Syndrome Scale score	38.6±7.3	37.9±8.5	0.641

* Data are presented as mean ± standard deviation or No. (%) of participants; total may not equal 100% because of missing data.

TABLE 2. Clinical and biochemical variables after 12 weeks of treatment

Variables	Berberine (n=58)		Placebo (n=55)		P value
	Mean (95% confidence interval)	P value (vs baseline)	Mean (95% confidence interval)	P value (vs baseline)	
Net weight gain, kg					
Week 3	0.27 (-0.17, 0.70)	0.115	0.15 (-0.30, 0.60)	0.452	0.720
Week 6	-0.32 (-0.77, 0.12)	0.178	0.10 (-0.36, 0.56)	0.715	0.196
Week 9	-0.47 (-0.95, 0.01)	0.094	0.28 (-0.20, 0.74)	0.338	**0.031**
Week 12	-0.71 (-1.19, -0.23)	**0.017**	0.37 (-0.10, 0.84)	0.223	**0.002**
Change in body mass index, kg/m^2					
Week 3	-0.09 (-0.07, 0.24)	0.153	0.07 (-0.09, 0.23)	0.331	0.894
Week 6	-0.13 (-0.29, 0.03)	0.139	0.04 (-0.12, 0.20)	0.682	0.140
Week 9	-0.19 (-0.36, -0.02)	0.068	0.10 (-0.06, 0.27)	0.327	**0.018**
Week 12	-0.27 (-0.44, -0.10)	0.012	0.13 (-0.03, 0.30)	0.218	**0.001**
Change in waist circumference, cm					
Week 3	0.45 (-0.49, 1.38)	0.335	-0.07 (-1.02, 0.88)	0.832	0.454
Week 6	0.29 (-0.66, 1.23)	0.587	-0.82 (-1.79, 0.15)	0.161	0.111
Week 9	-0.28 (-1.33, 0.77)	0.716	-0.86 (-1.86, 0.15)	0.176	0.439
Week 12	-1.48 (-2.51, -0.45)	**0.034**	-1.13 (-2.12, -0.14)	0.081	0.635
Systolic blood pressure, mmHg					
Baseline	125.1 (122.6, 127.7)	-	124.6 (122.0, 127.2)	-	0.772
Week 6	124.3 (121.6, 127.1)	0.632	124.4 (121.6, 127.2)	0.916	0.970
Week 12	122.7 (119.7, 125.7)	0.213	125.5 (122.7, 128.3)	0.636	0.185
Diastolic blood pressure, mmHg					
Baseline	78.0 (76.2, 79.8)	-	77.4 (75.6, 79.2)	-	0.625
Week 6	77.8 (75.8, 79.7)	0.825	75.6 (73.6, 77.5)	0.137	0.119
Week 12	74.3 (72.2, 76.4)	**0.007**	77.8 (75.8, 79.8)	0.775	**0.019**
Triglycerides, mmol/L					
Baseline	2.19 (2.02, 2.36)	-	2.18 (2.01, 2.36)	-	0.949
Week 6	1.95 (1.76, 2.14)	**0.038**	1.93 (1.74, 2.13)	**0.034**	0.901
Week 12	1.89 (1.69, 2.09)	**0.021**	2.12 (1.93, 2.32)	0.629	0.101
Total cholesterol, mmol/L					
Baseline	5.18 (5.08, 5.28)	-	5.14 (5.04, 5.24)	-	0.569
Week 6	4.61 (4.50, 4.72)	**<0.0001**	5.15 (5.03, 5.26)	0.900	**<0.0001**
Week 12	4.61 (4.49, 4.73)	**<0.0001**	5.19 (5.07, 5.30)	0.509	**<0.0001**
High-density lipoprotein cholesterol, mmol/L					
Baseline	1.23 (1.20, 1.26)	-	1.24 (1.21, 1.27)	-	0.599
Week 6	1.16 (1.13, 1.19)	**0.001**	1.22 (1.19, 1.25)	0.303	**0.016**
Week 12	1.19 (1.16, 1.22)	0.094	1.22 (1.19, 1.26)	0.476	0.179
Low-density lipoprotein cholesterol, mmol/L					
Baseline	3.20 (3.11, 3.30)	-	3.14 (3.04, 3.25)	-	0.402
Week 6	2.74 (2.63, 2.85)	**<0.0001**	3.24 (3.13, 3.35)	0.144	**<0.0001**
Week 12	2.73 (2.61, 2.84)	**<0.0001**	3.24 (3.13, 3.35)	0.179	**<0.0001**
Fasting blood glucose, mmol/L					
Baseline	5.72 (5.50, 5.93)	-	5.66 (5.44, 5.88)	-	0.739
Week 6	5.33 (5.08, 5.57)	**0.009**	5.88 (5.63, 6.12)	0.150	**0.002**
Week 12	5.43 (5.17, 5.68)	0.087	5.57 (5.33, 5.82)	0.587	0.422
Glycated haemoglobin, %					
Baseline	5.94 (5.89, 6.00)	-	5.91 (5.86, 5.97)	-	0.446
Week 6	5.84 (5.77, 5.90)	0.006	5.90 (5.84, 5.97)	0.822	0.133
Week 12	5.80 (5.74, 5.87)	**0.001**	5.89 (5.83, 5.96)	0.662	**0.050**

group displayed greater decreases in BMI at 9 weeks (P=0.018) and 12 weeks (P=0.001), lower levels of total cholesterol and LDL cholesterol at 6 and 12 weeks (all P<0.0001), lower levels of HDL cholesterol (P=0.016) and FBG (P=0.002) at 6 weeks, lower levels of diastolic blood pressure (P=0.019) and HbA1c (P=0.016) at 12 weeks.

There were no significant differences in total and subscale scores on the Positive and Negative Syndrome Scale or the Extrapyramidal Symptom Rating Scale–Abbreviated, either within or between groups (data not shown). The berberine group had a lower incidence of drowsiness than the placebo group (P=0.008). No serious adverse events were reported.

Discussion

In patients with SSD experiencing typical MetS, berberine adjunctive treatment for 12 weeks led to reductions in body weight, BMI, diastolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, FBG, and HbA1c. Berberine had no effects on psychotic symptoms or involuntary movement symptoms. Participants receiving berberine had a lower incidence of drowsiness than those receiving placebo, suggesting that berberine can be used to manage sleep disturbances that often occur during antipsychotic treatment. These results confirm the weight-lowering and anti-MetS effects of berberine in patients with SSD who are receiving antipsychotic therapy.

Berberine adjunctive treatment led to 0.75 kg weight loss at 6 weeks and 1.08 kg weight loss at 12 weeks. These results are comparable with the 1.0 kg weight loss observed in patients with diabetes mellitus after 3 months of berberine treatment. In another study, approximately 2 kg weight loss was observed in patients with non-alcoholic fatty liver disease after 16 weeks of berberine treatment. The weight-lowering effect of berberine may be enhanced by extending the duration of treatment. The WC of participants on berberine was substantially lower at the end of the study, suggesting that berberine can help control central obesity.

Although berberine did not exacerbate psychotic symptoms or involuntary movement symptoms, there were more dropouts in the berberine group than in the placebo group (29.3% vs 14.5%). The main dropout reasons were inability to adhere to the treatment schedule and personal reasons, rather than berberine intolerance. No serious adverse events were reported during the study period. The findings suggest that berberine is a safe, orally administered agent.[4]

There were several limitations in the present study. First, the dropout rate of 22.1% was relatively high, but it is acceptable for a clinical analysis of patients with schizophrenia. Second, although baseline antipsychotic and other medication profiles were similar in the two groups, heterogeneous medication regimens could have led to inconsistent MetS severity. Further analysis is needed to determine whether the anti-MetS efficacy of berberine is associated with specific antipsychotic regimens. Third, the fixed berberine dosage was based on previous studies, in which the dosages ranged from 0.6 g to 1.5 g per day. Further investigations may be necessary to optimise the berberine dose for MetS. Fourth, the long-term efficacy of berberine was not evaluated. Long-term studies with larger sample sizes are needed to confirm the findings of this study.

Conclusion

Berberine effectively reduces antipsychotic-associated weight gain and improves MetS without exacerbating psychotic symptoms or inducing adverse effects.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#14151891). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

Disclosure

The results of this research have been previously published in:

1. Chan M, Qin Z, Man SC, et al. Adjunctive berberine reduces antipsychotic-associated weight gain and metabolic syndrome in patients with schizophrenia: a randomized controlled trial. Psychiatry Clin Neurosci 2022;76:77-85.

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Chinese versus western medicine for threatened miscarriage: abridged secondary publication

CC Wang *, ZX Lin, TC Li, XK Wu

KEY MESSAGES

1. Effects of Chinese medicine and a combination of Chinese and western medicine on clinical pregnancy, ongoing pregnancy, live birth, and miscarriage were investigated.
2. The sample size was insufficient to detect beneficial or harmful effects.
3. A larger-scale multicentre trial may provide more conclusive results.

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Introduction

Therapies for threatened miscarriage are empirical, and their efficacies in preventing miscarriage are unclear. Combinations of Chinese medicines (CM) and pharmaceuticals may be useful in the management of threatened miscarriage. We compared a modified classical CM formula with western medicine (WM) in terms of efficacy and safety among women with threatened miscarriage.

Methods

This study enrolled women aged 18 to 35 years with viable pregnancy complicated by threatened miscarriage in early gestation. Participants were randomised into four groups to receive the following treatments until 12 weeks of gestation: CM + WM placebo, CM placebo + WM, CM + WM, or CM placebo + WM placebo. The primary outcome was live birth. Secondary outcomes were clinical pregnancy, ongoing pregnancy, miscarriage, and adverse effects.

Results and discussion

In total, there were 200 participants; 196 completed the follow-up assessments and were included in the analysis. Participants in all four groups were comparable in terms of age, body mass index, gestational age, previous live birth rate, and miscarriage rate. Participants in the CM + WM group displayed slight (but not significant) increases in live birth, clinical pregnancy, and ongoing pregnancy rates; they also displayed a slight (but not significant) decrease in miscarriage rate. Participants in all four groups were comparable in terms of hormonal profile and quality of life. There were no serious adverse events; only unrelated minor adverse events were recorded. The sample size was insufficient to detect beneficial or harmful effects of CM and a combination of CM and WM in terms of preventing miscarriage during early pregnancy. Studies with larger sample sizes are warranted.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#15160971). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

Disclosure

The results of this research have been previously published in:

1. 高雅婷，博士學位論文，先兆流產的古今用藥分析及基於轉錄組測序探討壽胎丸安胎作用機制。浙江中醫藥大學2020年6月
2. Li L, Tang LY, Liang B, et al. Evaluation of in vitro embryotoxicity tests for Chinese herbal medicines. Reprod Toxicol 2019;89:45-53.

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Promotion of human papillomavirus vaccination among Chinese men who have sex with men: abridged secondary publication

Z Wang *, JTF Lau, PPK Lam, P Chan, F Fong, PKH Mo

KEY MESSAGES

1. A theory-based online tutorial plus brief motivational interviewing via phone was effective in increasing the uptake of three doses of the human papillomavirus (HPV) vaccine over a 24-month follow-up period among men who have sex with men in Hong Kong.
2. Changes in perceived susceptibility to HPV/HPV-related diseases and perceived barriers to HPV vaccination during the follow-up period led to the behavioural change.
3. The intervention was integrated into existing human immunodeficiency virus (HIV) testing and counselling services implemented by a non-governmental organisation focused on HIV prevention in Hong Kong.

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Introduction

Human papillomavirus (HPV) can cause genital warts and penile/anal cancer in men.[1] Men who have sex with men (MSM) are at higher risks of contracting HPV and related diseases.[2] Vaccination for HPV is highly effective in preventing genital warts and cancers in MSM; thus, MSM aged ≤45 years are recommended to take HPV vaccination.[3,4] However, HPV vaccine uptake is very low among MSM in Hong Kong. We used an online tutorial based on the Health Belief Model (HBM), combined with motivational interviewing (MI),[5] to promote HPV vaccine uptake among MSM in Hong Kong.

This study aimed to evaluate the efficacy of two online theory-based interventions with and without brief MI via phone in increasing the rate of complete HPV vaccination (ie, three doses) within a 24-month follow-up period among Hong Kong Chinese MSM.

Methods

This study was conducted between July 2017 and December 2019. Individuals eligible to participate in this study were Hong Kong Chinese-speaking men aged 18 to 45 years who self-reported having engagement in oral or anal intercourse with at least one man in the past 6 months, had no intention to leave Hong Kong for more than 1 consecutive month within the next 9 months, had regular Internet access, and were willing to be followed up by phone. Individuals who had received any HPV vaccine were excluded. Participants were recruited through outreach in gay bars/saunas, along with online solicitation and peer referral. Participant eligibility was confirmed by fieldworkers either on site or through telephone/social media. Verbal informed consent was obtained from each participant to maintain anonymity.

After completion of the baseline survey, participants were randomly assigned to the control group, health communication (HC) group, or HC plus MI (HC-MI) group. Participants were followed up at 3, 6, 9, and 24 months. In the HC intervention, participants completed a 20-minute self-administered online tutorial. They watched a 5-minute online video, in which a peer MSM discussed the high risk and serious consequences of penile/anal cancers, as well as the efficacy of HPV vaccination and its duration of protection. Brief alarming images of genital warts, penile cancers, and anal cancers were displayed to increase perceived severity. HPV vaccination was emphasised as a valuable long-term investment, and HPV vaccination procedures were demonstrated. Participants then answered self-administered online multiple-choice questions and performed a short exercise to modify relevant perceptions. In the MI intervention, participants received brief MI via phone. Reminders were sent to participants in the HC and HC-MI groups at 1, 2, 4, 6, and 8 months. Participants in the control group received online health-focused messages unrelated to HPV or HPV vaccination, without any reminders. Participants were given discount coupons (10% discount off the market price of HK$3800 [US$490] for three doses) to take HPV vaccination at a collaborating private clinic. Participants also could choose to take HPV vaccination elsewhere.

The primary outcome was validated completion

of HPV vaccination within the 24-month follow-up period. Secondary outcomes were changes in the four-item Perceived Susceptibility Scale, the two-item Perceived Severity Scale, the five-item Perceived Benefits Scale, the six-item Perceived Barriers Scale, the two-item Cues to Action Scale, and the three-item Perceived Self-Efficacy Scale. Participants who had not received any dose of the HPV vaccine at 24 months were asked about their willingness to receive three doses of the HPV vaccine in the next year.

Logistic regression models (for categorical outcomes) and linear regression models (for continuous outcomes) were used to examine between-group differences, after adjusting for background variables (ie, variables that differed [P<0.20] between groups at baseline). Adjusted odds ratios (AORs) and adjusted standardised coefficients (β values) were obtained. The Baron and Kenny's method was used to determine whether changes in HBM constructs (24 months vs baseline) mediated the intervention effect. P values <0.05 were considered statistically significant.

Results

In total, 624 participants completed the baseline survey. They were randomly assigned to the control group (n=208), HC group (n=208), or HC-MI group (n=208). Among the participants, 504 (80.8%) were followed up at 3 months, 472 (75.6%) were followed up at 6 months, 439 (70.4%) were followed up at 9 months, and 459 (73.6%) were followed up at 24 months. The three groups were comparable in terms of all baseline characteristics, except for anal intercourse with regular male sex partners (P=0.03) and the Perceived Barriers Scale score (P=0.03). Adjustments were performed to control for these two background variables in subsequent analyses (Table 1). The loss-to-follow-up rate at 24 months was 24.5% in the control group, 31.3% in the HC group, and 23.6% in the HC-MI group. In a comparison of participants who were followed up and participants who were lost to follow-up at 24 months, there were significant differences with respect to current marital status, education level, anal intercourse with non-regular male sex partners, condomless anal intercourse with men, multiple male sex partners, sexualised drug use, and sexual potency drug use.

Among participants who had not taken any HPV vaccination at 24 months, more participants in the HC-MI group indicated that they intended to receive three doses of the HPV vaccine in the next year, compared with participants in the control group (23.3% vs 16.1%, AOR=1.49, 95% confidence interval [CI]=1.17-1.91, P=0.001, Table 2). In total, 75 participants had receipts to confirm completion of full HPV vaccination at 24 months. The HC-MI group had higher HPV vaccination uptake than the control group (17.3% vs 7.2%, AOR=1.57, 95% CI=1.14-2.17, P=0.006; Table 3). However, after adjusting for changes in perceived susceptibility, the association between intervention status and completion of HPV vaccination was not significant (AOR=1.42, 95% CI=0.99-2.03, P=0.06), whereas changes in perceived susceptibility remained strongly associated with intervention status (AOR=1.23, 95% CI=1.12-1.35, P<0.001). The association between intervention status and completion of HPV vaccination was weakened (from P<0.001 to P=0.05) after adjusting for changes in perceived barriers, which remained significant (P<0.001). A partial mediation effect was observed (Table 3).

Discussion

The combination of an online tutorial plus MI via phone led to a significant increase in the uptake of the three required doses of the HPV vaccine among MSM during the follow-up period. The use of an online tutorial alone did not significantly improve vaccine uptake, compared with the control group. Moreover, the addition of MI to the online tutorial approach did not demonstrate greater efficacy, compared with the use of an online tutorial alone. The lack of statistical significance may be related to an inadequate sample size and limited statistical power. Until further evidence is generated, we recommend using the combination of an online tutorial plus MI to promote HPV vaccination among MSM in Hong Kong. Our mediation analysis showed that perceived susceptibility and perceived barriers were theoretical components associated with behavioural changes. These findings extend the applicability of the HBM.

Hong Kong experienced a shortage of 9-valent HPV vaccines from May to December 2018. This unexpected event overlapped with the second half of the follow-up period and affected some participants. The supply rapidly resumed after December 2018; most participants had already received the first dose before the unexpected event, and the follow-up period was extended from 9 months to 24 months; thus, we assumed that the impact of this event on the primary outcome and internal validity was limited.

The present study, which was theory-based and supported by the results of exploratory analyses, had a long follow-up duration, low dropout rate, and well-validated primary outcome. The positive process evaluation results indicated that the intervention was well-received. However, this study had some limitations. First, the intervention was limited to MSM with Internet access. Second, our findings may not be generalisable to other Chinese cities. Third, attrition bias may have been present. Fourth, no information was collected regarding MSM who refused to participate. Fifth, MI sessions were not evaluated by audiotaping, which is considered the gold standard approach for fidelity assessment.

TABLE 1. Baseline characteristics of participants in control, health communication (HC), and HC plus motivational interviewing (HC-MI) groups

	Control group (n=208)*	HC group (n=208)*	HC-MI group (n=208)*	P value
Sociodemographic characteristics				
Age group, y				
18-26	65 (31.3)	73 (35.1)	64 (30.8)	0.57
27-36	101 (48.6)	91 (43.8)	91 (43.8)	
37-45	42 (20.2)	44 (21.2)	53 (25.5)	
Current marital status				
Single	171 (82.2)	162 (77.9)	177 (85.1)	0.24
Cohabiting with/married to a man	35 (16.8)	45 (40.5)	31 (14.9)	
Cohabiting with/married to a woman	2 (1.0)	1 (0.5)	0 (0.0)	
Education level				
Secondary or below	29 (13.9)	31 (14.9)	35 (16.8)	0.71
University or above	179 (86.1)	177 (85.1)	173 (83.2)	
Current employment status				
Full-time	166 (79.8)	165 (79.3)	161 (77.4)	0.82
Part-time/unemployed/retired/student	42 (20.2)	43 (20.7)	47 (22.6)	
Personal monthly income, HK$				
<10 000	32 (15.4)	36 (17.3)	33 (15.9)	0.38
10 000-19 999	74 (35.6)	71 (34.1)	62 (29.8)	
20 000-39 999	79 (38.0)	67 (32.2)	77 (37.0)	
≥40 000	21 (10.1)	34 (16.3)	35 (16.8)	
Refuse to disclose	2 (1.0)	0	1 (0.5)	
Sexual orientation				
Gay	179 (86.1)	189 (90.9)	189 (90.9)	0.31
Bisexual	28 (13.5)	19 (9.1)	19 (9.1)	
Heterosexual	1 (0.5)	0	0	
HIV/STI-related service utilisation in the past 6 months				
HIV testing				
No	93 (44.7)	98 (47.1)	87 (41.8)	0.55
Yes	115 (55.3)	110 (52.9)	121 (58.2)	
Other HIV/STI preventive services a				
No	102 (49.0)	109 (52.4)	113 (54.3)	0.55
Yes	106 (51.0)	99 (47.6)	95 (45.7)	
Sexual behaviours in the past 6 months				
Anal intercourse with regular male sex partners				
No	31 (14.9)	39 (18.8)	52 (25.0)	
Yes	177 (85.1)	169 (81.3)	156 (75.0)	0.03
Anal intercourse with non-regular male sex partners				
No	103 (49.5)	101 (48.6)	99 (47.6)	0.93
Yes	105 (50.5)	107 (51.4)	109 (52.4)	
Condomless anal intercourse with men				
No	133 (63.9)	139 (66.8)	132 (63.5)	0.74
Yes	75 (36.1)	69 (33.2)	76 (36.5)	
Multiple male sex partners				
No	90 (43.3)	92 (44.2)	95 (45.7)	0.88
Yes	118 (56.7)	116 (55.8)	113 (54.3)	

Abbreviations: HPV, human papillomavirus; MSM, men who have sex with men; STI, sexually transmitted infection

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

TABLE 1. (cont'd)

	Control group (n=208)*	HC group (n=208)*	HC-MI group (n=208)*	P value
Sexualised drug use				
No	193 (92.8)	198 (95.2)	194 (93.3)	0.56
Yes	15 (7.2)	10 (4.8)	14 (6.7)	
Sexual potency drug use				
No	193 (92.8)	197 (94.7)	193 (92.8)	0.66
Yes	15 (7.2)	11 (5.3)	15 (7.2)	
History of HIV/STI				
Self-reported HIV serostatus				
Negative	183 (88.0)	185 (88.9)	184 (88.5)	0.96
Positive	11 (5.3)	7 (3.4)	8 (3.8)	
Refuse to disclose	3 (1.4)	4 (1.9)	5 (2.4)	
Never tested for HIV antibodies	11 (5.3)	12 (5.8)	11 (5.3)	
History of other STI				
No	170 (81.7)	170 (81.7)	163 (26.1)	0.61
Yes	38 (18.3)	38 (18.3)	45 (21.6)	
Lifestyle characteristics				
Current smoker				
No	165 (79.3)	162 (77.9)	166 (79.8)	0.88
Yes	43 (20.7)	46 (22.1)	42 (20.2)	
Drinking in the past year				
No	39 (18.8)	28 (13.5)	36 (17.3)	0.32
Yes	169 (81.2)	180 (86.5)	172 (82.7)	
Knowledge related to HPV/HPV vaccination				
Both men and women can be affected by HPV				
Yes	156 (75.0)	174 (83.7)	163 (78.4)	
No	9 (4.3)	11 (5.3)	15 (7.2)	
Do not know	43 (20.7)	23 (11.1)	30 (14.4)	
HPV infection can cause STI				
Yes	129 (62.0)	144 (69.2)	135 (64.9)	
No	20 (9.6)	18 (8.7)	19 (9.1)	
Do not know	59 (28.4)	46 (22.1)	54 (26.0)	
HPV infection can cause cancers in men				
Yes	89 (42.8)	114 (54.8)	99 (47.6)	
No	34 (16.3)	37 (17.8)	37 (17.8)	
Do not know	85 (40.9)	57 (27.4)	72 (34.6)	
HPV can be totally cured by available treatments				
Yes	31 (14.9)	28 (13.5)	35 (16.8)	
No	110 (52.9)	132 (63.5)	112 (53.8)	
Do not know	67 (32.2)	48 (23.1)	61 (29.1)	
Effective HPV vaccination is available for men in Hong Kong				
Yes	113 (54.3)	131 (63.0)	110 (52.9)	
No	18 (8.7)	28 (13.5)	26 (12.5)	
Do not know	77 (37.0)	49 (23.6)	72 (34.6)	
No. of shots required to prevent HPV infection in men				
3	56 (26.9)	69 (33.2)	68 (32.7)	
Other answers/Do not know	152 (73.1)	139 (66.8)	140 (67.3)	

TABLE 1. (cont'd)

	Control group (n=208)*	HC group (n=208)*	HC-MI group (n=208)*	P value
No. of correct responses				
0	33 (15.9)	19 (9.1)	27 (13.0)	0.26
1-2	45 (21.6)	40 (19.2)	46 (22.1)	
3-4	100 (48.1)	104 (50.0)	95 (47.9)	
5-6	30 (14.4)	45 (21.6)	40 (19.2)	
Perceptions related to HPV/HPV vaccination based on the Health Belief Model				
Perceived susceptibility to HPV (% high/very high)				
Perceived risk of contracting HPV in lifetime	42 (20.2)	52 (25.0)	49 (23.6)	
Perceived risk of contracting genital warts in lifetime	39 (18.8)	51 (24.5)	47 (22.6)	
Perceived risk of developing penile/anal cancers in lifetime	20 (9.6)	25 (12.0)	21 (10.1)	
Perceived HPV infection rate among MSM in Hong Kong	63 (30.3)	53 (25.5)	55 (26.4)	
Perceived Susceptibility Scale score	10.8±3.0	10.9±3.3	10.4±3.5	0.38
Perceived severity of HPV-related diseases (% high/very high)				
Harmful effects of genital warts on physical health	119 (57.2)	119 (57.2)	128 (61.5)	
Harmful effects of penile/anal cancers on physical health	135 (64.9)	153 (73.6)	137 (65.9)	
Perceived Severity Scale score	7.6±1.9	7.7±1.7	7.5±1.8	0.59
Perceived benefit of HPV vaccination (% agree/strongly agree)				
HPV vaccination is highly effective in preventing HPV infection	143 (68.8)	166 (79.8)	147 (70.7)	
HPV vaccination is highly effective in preventing genital warts	142 (68.3)	151 (72.6)	138 (66.3)	
HPV vaccination is highly effective in preventing penile/anal cancers	129 (62.0)	138 (66.3)	123 (59.1)	
HPV vaccination provides long-term protection	104 (50.0)	113 (54.3)	105 (50.5)	
HPV vaccination provides peace of mind	142 (68.3)	127 (61.1)	139 (66.8)	
Perceived Benefits Scale score	18.9±3.1	18.9±2.9	18.6±2.9	0.58
Perceived barriers to HPV vaccination (agree/strongly agree)				
HPV vaccination is not worth the cost (HK$2000-3000)	64 (30.8)	44 (21.1)	38 (18.3)	
The procedures involved in HPV vaccination are complicated	33 (15.9)	30 (13.3)	17 (8.2)	
Severe adverse effects can occur after HPV vaccination	20 (9.6)	15 (7.2)	17 (8.2)	
HPV vaccination can cause embarrassment	25 (12.0)	20 (9.6)	18 (8.7)	
Others would think I was engaging in high-risk behaviours if I took HPV vaccination	33 (15.9)	25 (12.0)	25 (12.0)	
I would be stigmatised by service providers if I took HPV vaccination	18 (8.7)	15 (7.2)	13 (6.3)	
Perceived Barriers Scale score	13.5±5.2	12.6±4.0	12.4±4.2	0.03
Perceived cues to action related to HPV vaccination (% agree/strongly agree)				
Medical professionals suggest that I take HPV vaccination	3 (1.4)	6 (2.9)	7 (3.4)	
MSM peers suggest that I take HPV vaccination	8 (3.8)	15 (7.2)	5 (2.4)	
Cues to Action Scale score	2.7±1.3	2.9±1.5	2.8±1.4	0.56
Perceived self-efficacy related to HPV vaccination (% agree/strongly agree)				
The choice to take HPV vaccination is completely in my control	172 (82.7)	169 (81.3)	183 (88.0)	
I am confident that I could take HPV vaccination in the next year if I wanted to	142 (68.3)	139 (66.8)	147 (70.7)	
It would be easy for me to take HPV vaccination in the next year if I wanted to	154 (74.0)	145 (69.7)	153 (73.6)	
Perceived Self-Efficacy Scale score	12.6±2.4	12.4±2.6	12.6±2.4	0.61

TABLE 2. Between-group comparisons of control, health communication (HC), and HC plus motivational interviewing (HC-MI) groups

	Control group*	HC group*	HC-MI group*	HC group vs control group		HC-MI group vs control group		HC-MI group vs HC group	
				Adjusted odds ratio (95% confidence interval)	P value	Adjusted odds ratio (95% confidence interval)	P value	Adjusted odds ratio (95% confidence interval)	P value
Uptake of three doses of the HPV vaccine within 24 months	15/208 (7.2%)	24/208 (11.5%)	36/208 (17.3%)	1.61 (0.82-3.18)	0.17	1.57 (1.14-2.17)	0.006	1.55 (0.89-2.72)	0.13
Willingness to receive three doses of the HPV vaccine after 24 months among individuals who had not taken HPV vaccination	31/193 (16.1%)	29/184 (15.8%)	40/172 (23.3%)	0.94 (0.54-1.64)	0.82	1.49 (1.17-1.91)	0.001	1.63 (0.96-2.78)	0.07
Perceptions based on the Health Belief Model				**Adjusted β**	**P value**	**Adjusted β**	**P value**	**Adjusted β**	**P value**
Perceived Susceptibility Scale									
Baseline	10.8±3.0	10.9±3.3	10.4±3.5	0.01	0.91	-0.07	0.19	-0.06	0.22
24 months	10.6±3.1	10.5±3.5	11.0±3.4	-0.01	0.88	0.05	0.26	0.06	0.23
Change	-0.2±3.1	-0.3±3.5	0.5±3.8	-0.01	0.79	0.12	0.02	0.11	0.02
P value	0.29	0.19	0.05						
Perceived Severity Scale									
Baseline	7.6±1.9	7.7±1.7	7.5±1.8	0.04	0.37	0.01	0.82	-0.04	0.38
24 months	8.7±1.7	8.8±1.6	8.8±1.5	0.01	0.80	0.03	0.62	0.02	0.68
Change	1.2±1.9	1.1±1.7	1.3±1.9	-0.03	0.52	0.02	0.75	0.06	0.24
P value	<0.001	<0.001	<0.001						
Perceived Benefits Scale									
Baseline	18.9±3.1	18.9±2.9	18.6±2.9	-0.02	0.70	-0.06	0.20	-0.05	0.30
24 months	18.4±3.0	18.5±3.4	18.7±3.0	-0.001	0.98	0.03	0.53	0.02	0.69
Change	-0.5±3.4	-0.3±3.2	0.1±3.3	0.02	0.75	0.09	0.09	0.07	0.19
P value	0.04	0.12	0.82						
Perceived Barriers Scale									
Baseline	13.5±5.2	12.6±4.0	12.4±4.2	-0.10	0.05	-0.12	0.02	-0.03	0.60
24 months	15.0±4.6	13.4±4.3	12.5±4.1	-0.11	0.01	-0.21	<0.001	-0.10	0.02
Change	1.4±4.8	0.8±3.5	0.1±4.1	-0.12	0.01	-0.21	<0.001	-0.11	0.02
P value	<0.001	0.001	0.79						
Cues to Action Scale									
Baseline	2.7±1.3	2.9±1.5	2.8±1.4	0.06	0.26	0.02	0.68	-0.04	0.48
24 months	2.9±1.6	2.9±1.5	2.9±1.5	-0.004	0.93	0.01	0.78	0.01	0.87
Change	0.2±1.8	0.03±1.8	0.1±1.9	-0.05	0.34	-0.003	0.95	0.03	0.49
P value	0.14	0.79	0.27						
Perceived Self-Efficacy Scale									
Baseline	12.6±2.4	12.4±2.6	12.6±2.4	-0.08	0.10	-0.05	0.29	0.03	0.55
24 months	12.3±2.1	12.1±2.5	12.0±2.5	-0.06	0.22	-0.09	0.08	-0.04	0.45
Change	-0.3±2.5	-0.3±2.6	-0.6±2.8	0.02	0.66	-0.03	0.53	-0.06	0.23
P value	0.05	0.12	0.002						

Abbreviation: HPV, human papillomavirus

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

TABLE 3. Test for independent effects of changes in Health Belief Model scale scores on the association between intervention status (health communication plus motivational interviewing [HC-MI] group vs control group) and uptake of three doses of the human papillomavirus vaccine during the follow-up period (n=416)

Model	Variables	B	Standard error	Adjusted odds ratio (95% confidence interval)	P value
1	Intervention status (HC-MI group vs control group)	0.47	0.17	1.61 (1.14-2.26)	0.006
2A	Changes in Perceived Susceptibility Scale score	0.22	0.05	1.25 (1.14-1.38)	<0.001
3A	Intervention status (HC-MI group vs control group)	0.35	0.18	1.42 (0.99-2.03)	0.06
	Changes in Perceived Susceptibility Scale	0.21	0.05	1.23 (1.12-1.35)	<0.001
2B	Changes in Perceived Barriers Scale score	-0.18	0.04	0.84 (0.77-0.91)	<0.001
3B	Intervention status (HC-MI group vs control group)	0.37	0.18	1.44 (1.01-2.06)	0.05
	Changes in Perceived Barriers Scale score	-0.16	0.04	0.85 (0.79-0.92)	<0.001

Conclusion

The combination of a theory-based online tutorial plus brief MI via phone was effective in increasing completion of HPV vaccination among MSM in Hong Kong.

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Disclosure

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WhatsApp group discussion for smoking relapse prevention: a randomised controlled trial (abridged secondary publication)

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KEY MESSAGES

1. Compared with short message service, WhatsApp group discussion did not lead to a significant increase in long-term tobacco abstinence or a significant decrease in smoking relapse among recent quitters who received smoking cessation support.
2. The use of a WhatsApp group discussion was associated with short-term tobacco abstinence.

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Introduction

The maintenance of long-term smoking cessation (SC) is difficult because most quitters return to smoking.[1] According to a meta-analysis of 43 randomised controlled trials of pharmacological interventions for SC, <30% of smokers who received pharmacological interventions remained abstinent at the 1-year follow-up, and approximately 40% of individuals who quit relapsed within 1 year after treatment.[2] Online platforms accessed via mobile devices (mhealth) have been used to reduce smoking relapse rates by providing immediate assistance and interaction among group members.[3-5] A trial involving smokers with posttraumatic stress disorders showed that the use of mobile phone apps for relapse prevention was feasible and acceptable.[5] Smoking cessation messages sent directly by physicians to smokers via WhatsApp may increase the rate of quitting.[4] The use of WhatsApp to help participants communicate with each other may improve engagement and support among smokers.[6] For participants who encounter cravings and other withdrawal symptoms outside of the clinical setting, online platforms may facilitate access to support.[7] We assessed the effectiveness of WhatsApp group discussion for smoking relapse prevention, compared with a control group using a one-way short message service.

Methods

The study protocol was approved by the Hospital Authority Research Ethics Committee, and the study was conducted from October 2018 to January 2020. All adult smokers who attended a usual SC counselling session were invited to participate. The inclusion criteria were age ≥18 years, a habit of smoking at least 1 cigarette per day, enrolment or re-enrolment in SC treatment for <8 weeks, SC of 3 to 30 days, ability to communicate in Cantonese/Mandarin and read Chinese, and possession of a smartphone with a local network connection. Eligible smokers were randomly allocated (at a 1:1 ratio) to the control group (three one-way SMS messages/week for 8 weeks) or experimental group (interactive group discussion via WhatsApp and SMS text messages/videos/photos for 8 weeks). Qualitative interviews were conducted at the 12-month follow-up to collect opinions regarding the WhatsApp group intervention.

The primary outcome was biochemically validated tobacco abstinence at the 12-month follow-up. Secondary outcomes included validated tobacco abstinence at the 6-month follow-up, prevalence of self-reported 7-day and continuous abstinence throughout the study period, and relapse rate (ie, proportion of quitters who smoked at least five cigarettes over 3 consecutive days).

A generalised estimating equation model was used to summarise the intervention effect via risk ratios, with and without adjustment for baseline characteristics. The number of individuals needed to produce one additional quitter at 12 months compared with the control group was determined by taking the reciprocal of the risk difference between the two groups. A linear mixed model was used to

evaluate group, time, and group-by-time interaction effects on ancillary outcomes. The final generalised estimating equation model assessed the numbers of messages received and posted by each participant in the WhatsApp group, along with SC outcomes.

Results

In total, 928 participants were randomly assigned to the experimental group (n=469) or the control group (n=469). The mean age was 43.0±11.7 years, and >70% of the participants were men. Both groups had similar biochemically validated abstinence rates at the 6-month and 12-month follow-ups. In the experimental group, participants who posted ≥20 posts had higher validated abstinence rates at the 6-month follow-up, compared with participants in the control group (P<0.05). Qualitative interviews showed that the experimental group saved time and money with respect to intervention delivery and that peer support and moderator support were beneficial. However, some participants felt that relapse prevention was their responsibility alone and had minimal desire to socialise. Text mining revealed that the provision of quitting-related advice and support by moderators was facilitated by the WhatsApp group discussion. Quitters were more likely than smokers to share their experiences in seeking healthcare professional assistance and quitting methods. Unsupervised text mining revealed classifications similar to predefined contextual lexicons visualised in heat-maps.

Discussion

WhatsApp group intervention did not increase the rate of tobacco abstinence or reduce the rate of relapse in recent quitters. These results suggest that group-based intervention via WhatsApp is not superior to SMS text messaging in terms of preventing smoking relapse, which differs from the findings in our previous pilot study that showed the effectiveness of WhatsApp group intervention. The present study included smokers who had quit for 3 to 30 days, which was much shorter than the 8-week abstinence period in our previous study. During the intervention period, all participants received real-time SC treatment from healthcare providers. Therefore, WhatsApp intervention may not have had an additional effect. Furthermore, the relapse prevention messages via WhatsApp or SMS had a similar impact on SC. Nonetheless, in the experimental group, participants who posted ≥20 posts had higher validated abstinence rates at the 6-month follow-up, compared with participants in the control group (P<0.05). This finding highlights the importance of group engagement in quitting outcomes.

Some participants in the experimental group reported that the messages sent by moderators and the social and emotional support from moderators and peer smokers helped them to quit smoking and remain abstinent. However, other participants perceived quitting as a personal task; therefore, experiences shared by others did not influence their behaviour. Moreover, participants stated that messages in the group were not personalised, and the frequent pop-up messages interrupted daily life. These disadvantages may counteract the beneficial effects. Therefore, WhatsApp group interventions may be optimised by decreasing group discussion frequency, improving message content, and strengthening connections and interactions among group members.

This study had some limitations. First, participants were recent quitters receiving SC intervention from community-based SC clinics. Second, only the WhatsApp platform was used for intervention. Third, WhatsApp conversations contain large amounts of slangs or colloquial words.

Funding

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Disclosure

The results of this research have been previously published in:

1. Cheung YTD, Chan CHH, Ho KS, et al. Effectiveness of WhatsApp online group discussion for smoking relapse prevention: protocol for a pragmatic randomized controlled trial. Addiction 2020;115:1777-85.

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Meteorologically favourable zones for seasonal influenza A and B in Hong Kong: abridged secondary publication

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KEY MESSAGES

1. An accurate risk alert system for influenza epidemics may promote public awareness of the risk of influenza infection. We used a supervised discretisation approach to establish meteorologically favourable zones for influenza epidemics in Hong Kong.
2. Using laboratory-confirmed data from four hospitals in Hong Kong for the period 2004 to 2019, we demonstrated satisfactory classification performance of meteorologically favourable zones based on ambient temperature and relative humidity. The performance was validated by the use of influenza-like illness plus, which is a combined metric comprising clinical diagnosis and laboratory data.
3. Favourable zones for influenza A involved either high temperatures and high humidity in the hot season, or low temperatures in the cold season, whereas favourable zones for influenza B simply required cold conditions.
4. Our findings may help public health and meteorology officials to establish a meteorology-based warning system for increased influenza activity.

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Introduction

Seasonal influenza causes a substantial disease burden each year. Influenza seasonality differs across climate zones. In temperate regions, influenza seasonality exhibits a consistent unimodal peak in winter. In tropical and subtropical regions, influenza seasonality exhibits a more diverse pattern. Influenza A and B are associated with different meteorological parameters.[1] In Hong Kong, influenza exhibits a bimodal seasonality, with one peak in winter and spring and another peak in summer. Some meteorological zones are more favourable for influenza activity.[2] This study was conducted to identify meteorologically favourable zones for influenza A and B, which would facilitate preparation for periods of increased demand for healthcare facilities.

Methods

We collected the weekly detection rates of laboratory-confirmed influenza A and B among inpatients admitted to four public hospitals in Hong Kong (Prince of Wales Hospital, Queen Elizabeth Hospital, Kwong Wah Hospital, and United Christian Hospital) between 1 January 2004 and 31 December 2019. We also performed an analysis of influenza-like illness plus (ILI+), which is a metric comprising the weekly viral detection rate and ILI+ count to validate our findings. We included data regarding inpatients admitted for upper respiratory tract infections, based on International Classification of Diseases (version 9) codes 460 to 487.

An influenza epidemic was defined as a period when influenza activity was above the 50th percentile in a year (ie, from week 44 to week 43 in the following year). To reduce stochastic variation in case detection, we included the two adjacent weeks (1 week before and 1 week after) in each epidemic period. Meteorologically favourable zones were defined as intervals in which meteorological variables had optimal performance in predicting influenza epidemics.

Meteorology records for the included hospitals were collected from their nearest weather stations. Meteorological data including weekly mean ambient temperature, relative humidity, and total rainfall were matched to the time periods covered by influenza data. Actual vapour pressure was used as a proxy for absolute humidity. Additionally, weekly mean concentrations of air pollutants (carbon monoxide, nitrogen dioxide, ozone, sulphur dioxide, and fine

particulate matter) were collected from the website of the Environmental Protection Department. The locations of air quality monitoring stations were matched to the locations of the corresponding hospitals. Because school closures are commonly used as public health interventions to interrupt influenza transmission within a community, records of school closures were collected from school calendars for the study period; the school closure variable was regarded as an indicator in the analysis.

We used classification and regression trees as a supervised discretisation approach to discretise continuous variables to intervals that can optimise prediction algorithm performance.[3] Because two influenza peaks were observed in each year, we developed an ensemble model of classification and regression trees stratified by hot season (ie, weeks 13 to 44) and cold season (ie, week 45 to week 12 in the next year); we developed separate models for influenza A and both influenza types. We established a receiver operating characteristic curve to evaluate the discriminating powers of meteorologically favourable zones; we used area under the curve (AUC) as the prediction endpoint for model optimisation. Prediction performance was considered good, excellent, and outstanding when the AUC was 0.7-0.8, 0.8-0.9, and >0.9, respectively. The cut-off point nearest to the top-left portion of the receiver operating characteristic curve was treated as a threshold to maximise the sensitivity and specificity of epidemic prediction. Data were divided into two sets: 2004 to 2014 (for the training model) and 2014 to 2019 (for the validation model). Evaluation statistics were derived for both datasets.

The primary analysis model included the predictors of ambient temperature and relative humidity, with a 3-week lag based on the typical duration of laboratory testing and reporting delay. Absolute humidity was used in the primary model because it is better than relative humidity in indicating influenza seasonality. We also evaluated prediction performance in terms of vulnerable age groups (0-4, 5-9, 10-14, and ≥65 years). To assess the validity of using the laboratory-confirmed rate of influenza as an indicator of influenza activity, the ILI+ rate was used in a separate analysis. Two additional models were established to identify potential improvements in prediction performance: (1) a full model including temperature, relative humidity, total rainfall, and all pollutants; and (2) a model including school closure as an indicator in the primary model using temperature and relative humidity. We also examined whether the results remained robust when the lag was set to 2 weeks and 4 weeks.

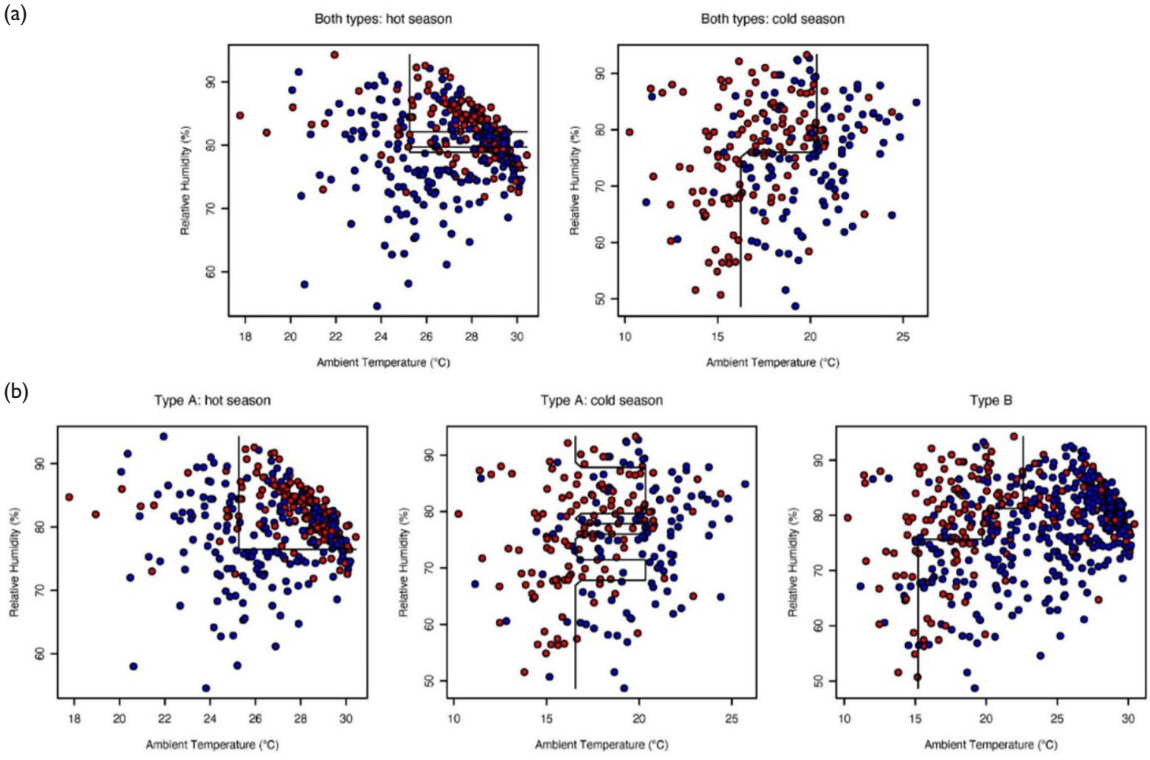

FIG 1. Scatter plots of influenza epidemics in different ambient temperature and relative humidity conditions for (a) both influenza types and (b) influenza A and B. Meteorologically favourable zones are used to classify epidemic weeks (red dots) and non-epidemic weeks (blue dots).

Results

In total, 392 epidemic weeks and 443 non-epidemic weeks were analysed. Using the primary model, meteorologically favourable zones based on mean temperature and relative humidity were established (Fig 1). Generally, temperature >25.1°C and relative humidity >79% were favourable conditions for an influenza epidemic in the hot season, whereas either (temperature <16.4°C) or (temperature <20.4°C with relative humidity >76%) was favourable condition for an influenza epidemic in the cold season. The training model had an AUC of 0.80 (95% confidence interval [CI]=0.76-0.83) with a sensitivity of 0.75 and a specificity of 0.74 for epidemic prediction (Fig 2). The validation model had an AUC of 0.71 (95% CI=0.65-0.77).

The training and validation models demonstrated similar AUCs of meteorologically favourable zones for influenza A in cold and hot seasons (Figs 1 and 2). Meteorologically favourable zones for influenza B were less consistent; the validation model exhibited an AUC of <0.7. The replacement of relative humidity with absolute humidity did not lead to apparent improvements in AUCs.

Meteorologically favourable zones were established for epidemic prediction in vulnerable age groups (Fig 3). Epidemic prediction performance varied among models, although the training model had an AUC >0.7. The classification of meteorologically favourable zones generally demonstrated good performance for prediction of influenza epidemics among individuals aged 0 to 4 years; the AUCs for both influenza types were 0.76 (95% CI=0.72-0.80) in the training model and 0.75 (95% CI=0.69-0.81) in the validation model. Decreased AUCs for epidemic prediction were observed when only influenza A or influenza B was considered. The classification of meteorologically favourable zones did not demonstrate good performance for age groups of 5 to 9 years, 10 to 14 years, and ≥65 years.

Our results remained robust when the outcome was modified to ILI+. A full model was developed using temperature, relative humidity, total rainfall, and pollutants; however, the validation model showed that AUCs of epidemic prediction were unsatisfactory, presumably because of increased complexity or model over-fitting. Inclusion of the school closure indicator did not improve epidemic prediction performance, compared with the primary model using temperature and relative humidity. Finally, epidemic prediction performance was not affected by 1-week changes in lag.

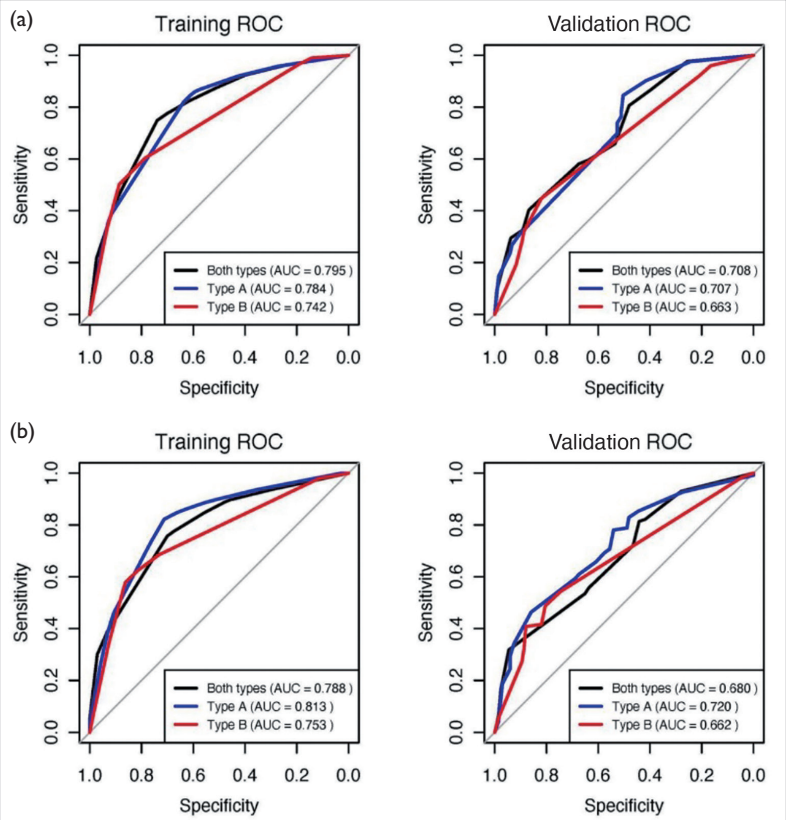

FIG 2. Receiver operating characteristic (ROC) curves established using training and validation data for (a) temperature and relative humidity and (b) temperature and absolute humidity.

Discussion

In the present study, we used a supervised discretisation approach to establish meteorologically favourable zones for influenza epidemics in Hong Kong. Using laboratory-confirmed data for the period 2004 to 2019, we showed that the classification performance of meteorologically favourable zones based on ambient temperature and relative humidity was excellent in the training model and good in the validation model. Compared with the results of a single-centre study conducted in Hong Kong in 2009,[2] our findings are generally consistent: favourable zones for influenza A involved either high temperatures and high humidity in the hot season or low temperatures in the cold season, whereas the favourable zone for influenza B simply required cold conditions. Our findings were supported by external validation (ie, ILI+ data); they could facilitate the establishment of an alert system for increased influenza activity.

Cold conditions were favourable for the activities of both influenza types. Indeed, cold weather is a common meteorological determinant of influenza seasonality in epidemiological and laboratory investigations[1,2,4] because it affects the frequency of indoor activity and the environmental stability for viral survival. However, the effect of relative humidity on influenza seasonality was less consistent. In the present study, the favourable zone

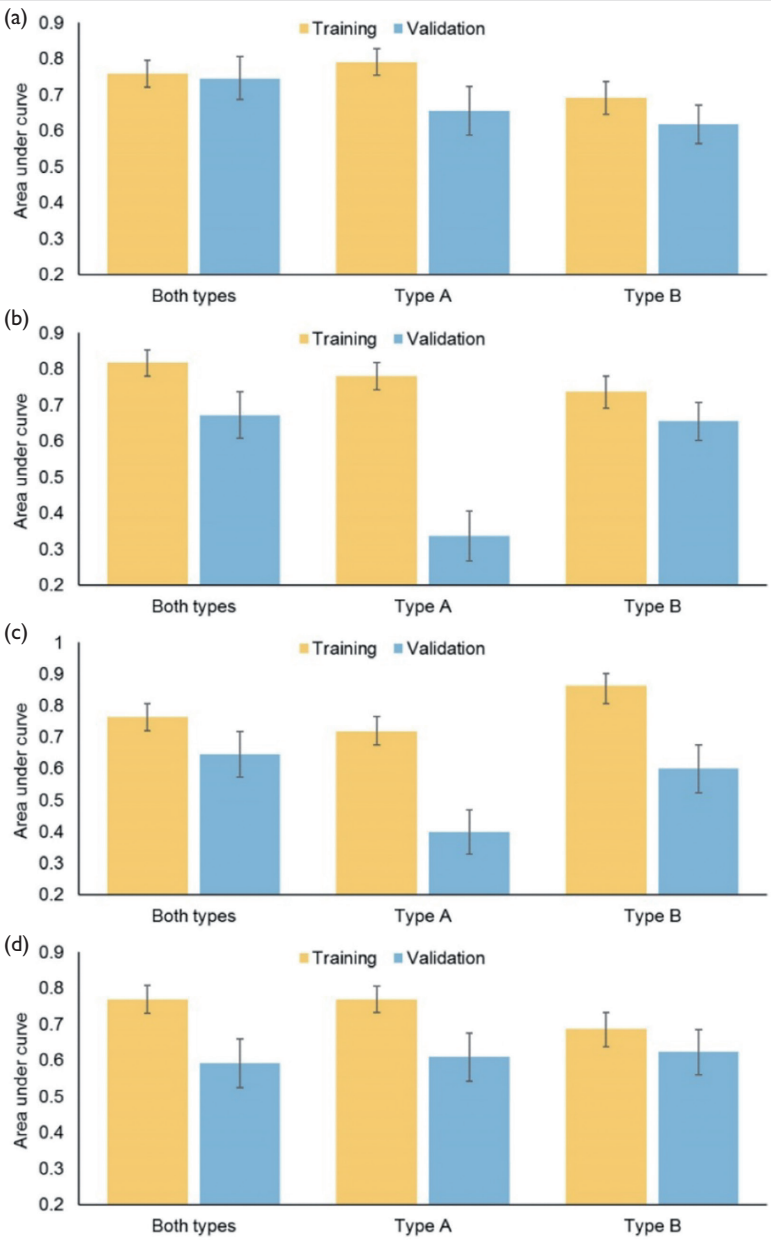

FIG 3. Areas under the curve of meteorologically favourable zones for both influenza types and influenza A and B, established using training and validation data, for epidemic prediction among age groups of (a) 0-4, (b) 5-9, (c) 10-14, and (d) ≥65 years.

of relative humidity differed according to influenza type, and the seasonal effect was affected by the dominant type of influenza in a particular year. In fact, relative humidity is not reliable to infer biological aspects of many organisms. For influenza viruses, absolute humidity has a stronger effect on transmission and survival. The effect of absolute humidity on influenza seasonality is more prominent in temperate settings but is attenuated in warmer climate settings (eg, subtropical regions).[5]

Despite satisfactory prediction performance overall, meteorologically favourable zones did not demonstrate good performance for age groups of 5 to 9 years, 10 to 14 years, and ≥65 years. We speculate that school children tend to have more social contacts than people in other age groups. Differences in contact patterns may influence the effect of meteorological conditions on viral transmission. Similarly, other covariates (eg, influenza-mediated exacerbation of chronic conditions) may affect influenza activity in older adults.

Conclusion

The classification performance of meteorologically favourable zones, established using ambient temperature and relative humidity, was satisfactory in Hong Kong. The performance was validated by the use of ILI+, which is a combined metric comprising clinical diagnosis and laboratory data. Our findings were supported by external validation, suggesting that meteorologically favourable zones could be used to establish an alert system for increased influenza activity. The system may promote infection risk awareness in the general public and ensure early preparation by healthcare officials for influenza season.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#19181132). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

Disclosure

The results of this research have been previously published in:

1. Chong KC, Chan PKS, Lee TC, et al. Determining meteorologically-favorable zones for seasonal influenza activity in Hong Kong. Int J Biometeorol 2023;67:609-19.

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B-cell signatures for disease flare and response to pre-emptive immunosuppressive therapy in patients with lupus nephritis: abridged secondary publication

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KEY MESSAGES

1. Pre-emptive increase in immunosuppression in patients with lupus nephritis experiencing asymptomatic serological reactivation can reduce renal relapse and is well-tolerated.
2. B-cell signatures can be modulated by pre-emptive treatment in patients with lupus nephritis and may serve as biomarkers for treatment response monitoring.

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Introduction

Lupus nephritis (LN) is a serious organ manifestation in patients with systemic lupus erythematosus (SLE) and a robust predictor for adverse clinical outcomes. Clinical relapses are common and associated with poor long-term renal prognosis. In patients with LN, prediction and prevention of clinical relapses are challenging. Serological reactivation often occurs after achieving renal remission and may precede clinical relapses; however, LN may be clinically quiescent in some patients despite experiencing serological reactivation. The use of conventional serological parameters (eg, levels of anti-double-stranded DNA [dsDNA] antibodies and complement) in guiding management decisions remains controversial. Therefore, management of asymptomatic serological reactivation (ASR) is an important clinical consideration.

Changes in B cell-related cytokines such as B-cell activation factor (BAFF), interleukin (IL)-6, IL-10, and IL-21 have been observed in patients with SLE, particularly during active disease.[1] These cytokines have pivotal roles in the differentiation/maturation and survival of various B-cell subsets.[1] Transcription repressors such as BTB domain and CNC homologue (BACH)1, BACH2, and paired box (PAX)5 are key regulators of B cell/plasma cell differentiation and maturation.

In our previous studies, pre-emptive increase in immunosuppression in patients with LN experiencing ASR was associated with a lower risk of renal relapse and a slower decline in renal function; it also was well-tolerated.[2] B-cell signatures including BACH1, BACH2, and PAX5 were associated with disease relapse in patients with LN.[3] We conducted a prospective randomised controlled trial to investigate the efficacy and safety of pre-emptive treatment in patients with LN experiencing ASR, and to determine whether B-cell signatures could be used to guide this management approach.

Methods

Recruited patients were randomly assigned to either the pre-emptive treatment group or the control group. In the pre-emptive treatment group, prednisolone was increased to 0.4 to 0.5 mg/kg/day, tapered by 5 mg every 2 weeks to reach 15 mg/day, then reduced by 2.5 mg every 2 weeks to reach 5 to 7.5 mg/day after 12 weeks. The second agent was adjusted as follows. For patients who received azathioprine <100 mg/day, the dose was increased to 100 mg/day. For patients who received mycophenolate mofetil <1.5 g/day, the dose was increased to 1.5 g/day. The dosages of azathioprine and mycophenolate mofetil remained at 100 mg/day and 1.5 g/day, respectively, for 12 weeks after treatment intensification; the dosages were subsequently tapered according to clinical status. Patients without serological remission after a course of pre-emptive treatment were closely monitored for renal function, urine microscopy, proteinuria, anti-dsDNA antibody level, and C3 level at 4-week intervals for up to 12 months. In the control group, the current immunosuppressive treatment regimen and dosage were not modified until the onset of renal or extra-renal flares.

To quantify the expression of BACH1, BACH2, and PAX5, lymphocytes were isolated by the Ficoll gradient method; B-cell subsets were stained with appropriate monoclonal antibodies (naïve B cells: $CD20^+CD27^-$, memory B cells: $CD20^+CD27^+$) and isolated by cell sorting. mRNA was extracted from naïve and memory B cells, then measured by

quantitative polymerase chain reaction. To quantify serum cytokines, the levels of BAFF, IL-6, and IL-10 were determined by enzyme-linked immunosorbent assays using standard methods.

Primary outcomes were the incidences of renal and extra-renal flares in patients with LN experiencing ASR who had or had not received pre-emptive treatment, and changes in B-cell subsets and relevant regulatory genes (BACH1, BACH2, PAX5), serum and urine cytokine profiles, and miRNA148a levels in patients who had or had not received pre-emptive treatment. Secondary outcomes were associations of B-cell signatures with subsequent renal or extra-renal flares, and associations of B-cell signatures with clinical parameters (anti-dsDNA antibody level, C3/4 level, renal function, proteinuria, and Systemic Lupus Erythematosus Disease Activity Index) at 12 months.

Results

In total, 43 patients with LN experiencing ASR were randomly assigned to the pre-emptive treatment group (n=20) or the control group (n=23) [Table]. Compared with the control group, the pre-emptive treatment group had lower incidences of clinical flares (10.0% vs 34.8%, P=0.028) and renal flares (0% vs 13.0%, P=0.047) during subsequent follow-up. The incidence of extra-renal flares did not differ between the two groups (P>0.05).

In the pre-emptive treatment group, the anti-dsDNA antibody level began to decrease at 4 weeks and remained stable until 52 weeks. In the control group, the anti-dsDNA antibody level remained elevated until 24 weeks after recruitment, then decreased at 52 weeks. There were no significant differences in anti-dsDNA antibody levels at 4, 12, 24, or 52 weeks between two groups (all P>0.05). Additionally, the two groups did not differ in terms of C3 levels at baseline or at 4, 12, 24, or 52 weeks (all P>0.05).

Infectious complications occurred in two patients in the pre-emptive treatment group (one each had herpes zoster or urinary tract infection) and in four patients in the control group (one each had herpes zoster, pneumonia, upper respiratory tract infection, or urinary tract infection). All infectious episodes were successfully managed with appropriate antimicrobial agents. There was no case of new-onset diabetes mellitus in the pre-emptive treatment group.

The serum BAFF level in the pre-emptive treatment group initially declined at 4 weeks, then gradually increased to a near-baseline level (Fig 1). Compared with the control group, the pre-emptive treatment group had a significantly higher BAFF level at baseline (P=0.02) and 52 weeks (P=0.03), but there were no significant differences at 4, 12, or 24 weeks. There were no significant differences between the two groups in terms of serum IL-6 and IL-10 levels at baseline or at 4, 12, 24, or 52 weeks (all P>0.05).

TABLE. Clinical characteristics of patients with lupus nephritis experiencing asymptomatic serological reactivation who had or had not received pre-emptive treatment

	Pre-emptive treatment (n=20)*	Control (n=23)*	P value
No. of men/women	3/17	2/21	0.520
Age, y	50.7±12.3	47.5±12.1	0.401
Duration of systemic lupus erythematosus, y	23.5±8.7	18.6±9.9	0.097
Class of lupus nephritis			
Class III ± V or IV ± V	16 (80.0)	19 (82.6)	0.494
Class V	4 (20.0)	4 (17.4)	0.826
Maintenance treatment			
Prednisolone alone	6 (30.0)	7 (30.4)	0.975
Prednisolone + mycophenolate mofetil	10 (50.0)	13 (56.5)	0.669
Prednisolone + azathioprine	4 (20.0)	3 (13.0%)	0.538
Serum creatinine, μmol/L	80.3±22.7	69.4±22.9	0.137
Estimated glomerular filtration rate, mL/min/1.73m^2	74.7±15.9	84.0±10.8	0.067
Anti–double-stranded DNA antibodies, IU/mL	159.4±65.0	141.7±65.7	0.397
C3, mg/dL	84.1±27.3	85.2±23.5	0.892
C4, mg/dL	18.5±6.4	16.4±10.4	0.482

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

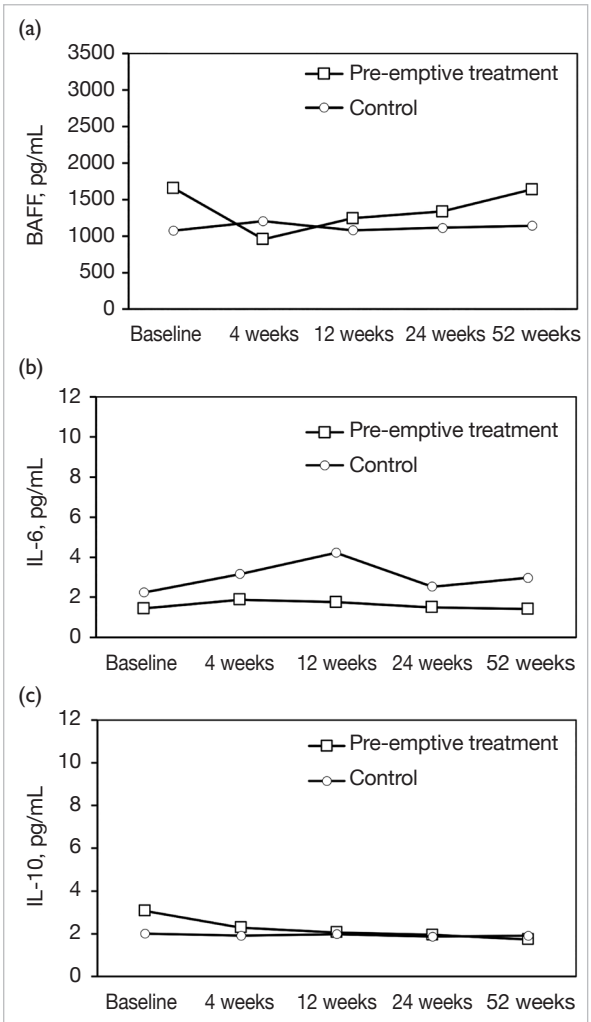

FIG 1. Changes in (a) B-cell activation factor [BAFF], (b) interleukin-6 (IL-6), and (c) interleukin-10 (IL-10) levels in patients with lupus nephritis experiencing asymptomatic serological reactivation who had or had not received pre-emptive treatment

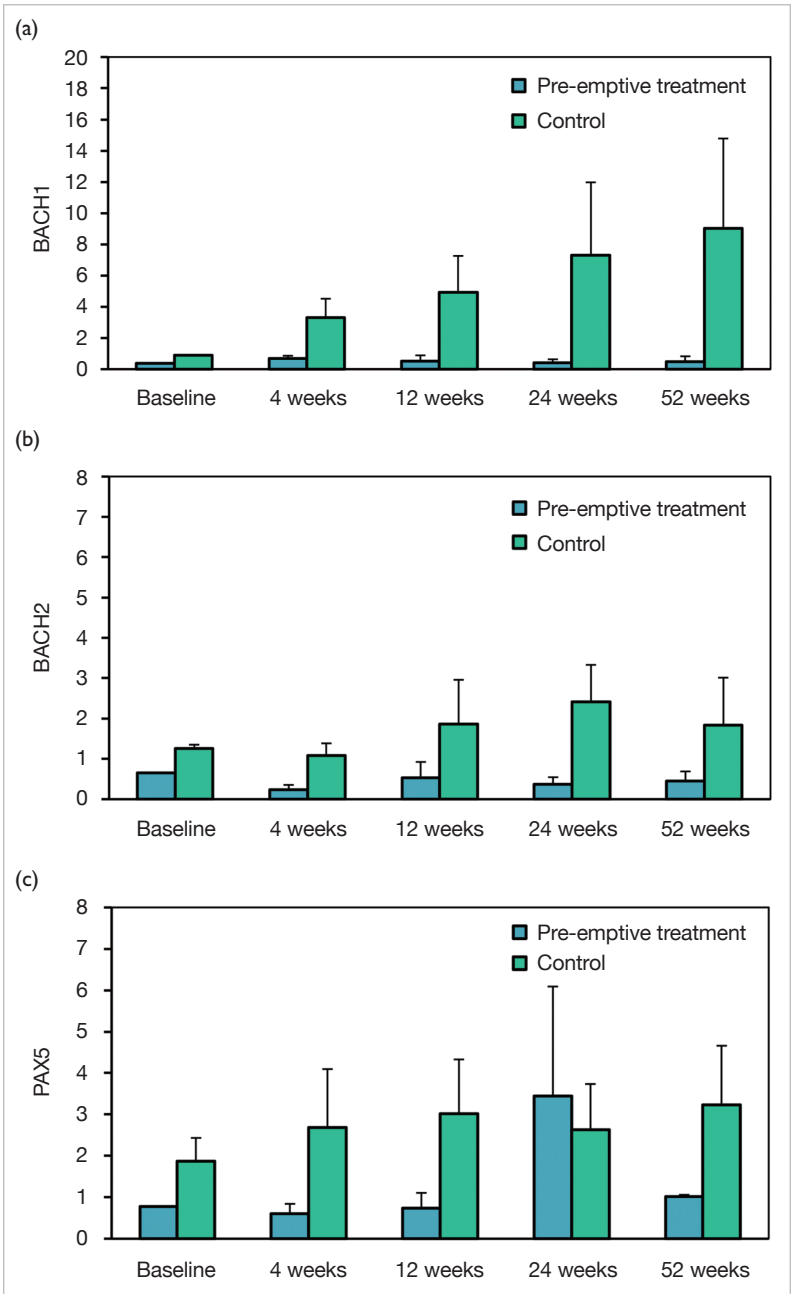

FIG 2. Changes in (a) BACH1, (b) BACH2, and (c) PAX5 expression levels in naive B cells from patients with lupus nephritis who had or had not received pre-emptive treatment

BACH1, BACH2, and PAX5 expression levels in naïve B cells remained stable in the pre-emptive treatment group. However, in the control group, these levels progressively increased over time (Fig 2). BACH1, BACH2, and PAX5 expression levels in naïve B cells were all lower (but not significantly) in the pre-emptive treatment group than in the control group at 4, 12, 24, and 52 weeks). In the pre-emptive treatment group, the BACH1 expression level in memory B cells was similar to the level in naïve B cells; although this level was lower (but not significantly) than that in the control group at 12, 24, and 52 weeks. In the pre-emptive treatment group, the BACH2 expression level in memory B cells increased from 4 weeks to 12 weeks, then decreased to a level similar to the that in the control group (all $P>0.05$). PAX5 expression in memory B cells did not significantly differ between the two groups.

Discussion

Pre-emptive increase in immunosuppression in patients with LN experiencing ASR effectively reduced the risks of clinical and renal relapse. This management approach was not associated with excess adverse effects. Our results were consistent with previous findings that pre-emptive increase in immunosuppression can mitigate impending renal flares in patients with LN experiencing ASR.[2] Nonetheless, our results did not show a benefit of

pre-emptive treatment in terms of preventing extra-renal flares.

The use of biomarkers is important to guide patient selection for pre-emptive treatment and treatment response monitoring. B-cell and B cell-related signatures are promising biomarkers for use in pre-emptive treatment. In the present study, the pre-emptive treatment group displayed a significantly higher BAFF level at baseline. This finding implies that B cells in the pre-emptive treatment group have greater immunological activity at baseline; the lower incidence of clinical flares suggests that this management approach is effective. Notably, there was an initial decline in the BAFF level at 4 weeks in the pre-emptive treatment group, followed by a gradual return to baseline as immunosuppression was tapered. Based on these observations, it remains unclear whether immunosuppression should be reduced more slowly to achieve a greater decrease in overall disease activity. There were no differences in IL-6 and IL-10 levels between the two groups, suggesting that these cytokines are not good biomarkers for patient selection and treatment response monitoring.

To further characterise the mechanistic aspect of pre-emptive treatment, we studied the effects of pre-emptive treatment on key B-cell transcription factors (ie, BACH1, BACH2, and PAX5). We demonstrated that pre-emptive treatment in patients with LN experiencing ASR was associated with increased BACH1, BACH2, and PAX5 expression levels in naïve B cells; it was also associated with increased BACH1 expression in memory B cells. BACH1 has key roles in immune responses and autoimmune conditions; it regulates the expression of core macrophage-associated genes. In a murine osteoarthritis model, BACH1 deficiency is associated with impaired development of antigen-presenting cells and partial protection from experimentally induced autoimmune encephalomyelitis; it was also associated with lower inflammation severity mediated by the upregulation of haem-oxygenase 1. BACH2 has dual effects on B cell homeostasis. In our previous study, BACH1, BACH2, and PAX5 expression levels in B lymphocytes were lower in patients with LN experiencing multiple relapses than in such patients who did not experience relapse.[3] BACH2 overexpression represses 'myeloid genes' in pre- and pro-B cells, hindering their progression to myeloid differentiation; rather, it promotes the commitment of those cells to the lymphoid lineage.[4] Other studies revealed that BACH2 expression was reduced in B cells isolated from patients with SLE; the transfection of BACH2 into B cells from such patients suppressed proliferation and augmented apoptosis. The exact role of BACH1 and BACH2 in SLE and LN remains poorly understood. A major limitation of the present study was the small sample size in each arm, which was related to patient recruitment difficulty during the COVID-19 pandemic. The follow-up duration was relatively short because of funding constraints. There is a need for additional studies regarding the effects of pre-emptive treatment on long-term renal function and disease stability in patients with LN experiencing ASR.

Funding

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Disclosure

The results of this research have been previously published in:

1. Yap DYH, Tang CSO, Chung HY, et al. A prospective randomized study on pre-emptive immunosuppressive treatment in lupus nephritis patients with asymptomatic serological reactivation. J Am Soc Nephrol 2020;31(Suppl):552.
2. Yap DYH, Tang CSO, Chung HY, et al. A prospective randomized study on pre-emptive immunosuppressive treatment in lupus nephritis patients with asymptomatic serological reactivation. Nephrol Dial Transplant 2020;35(Suppl 3):iii81-iii83.

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Risk prediction analytics for the Hong Kong Colorectal Cancer Screening Programme: abridged secondary publication

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KEY MESSAGES

1. Quantitative faecal immunochemical tests (FITs) contain diverse information that can be used to explore the epidemiology of colorectal cancer (CRC).
2. Using individuals' historical FIT results, we constructed and fitted a natural history model that had moderate predictive power for advanced colorectal neoplastic diseases but suboptimal predictive power for FIT positivity.
3. Our fitted natural history model provides an evidence-based analytical platform for future evaluation and optimisation of the cost-effectiveness of CRC screening. The use of a sex-specific threshold for FIT positivity could serve as a first step to modify the current screening algorithm.
4. The screening database should be linked to screenees' electronic health records to allow access to data regarding CRC risk factors, thereby enhancing predictive model performance and facilitating evaluations of personalised screening algorithms.
5. Policymakers should monitor participation and compliance rates, with prompt support for underserved populations.

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Introduction

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide. In the past few decades, CRC incidence and mortality have rapidly increased in Asia-Pacific countries such as China, Japan, South Korea, Australia, and Thailand. Many countries have implemented population-based CRC screening programmes.[1]

Colonoscopy is the gold standard for diagnosing colorectal neoplastic diseases. However, because of capacity constraints and potential adverse events associated with colonoscopy,[2] quantitative faecal immunochemical tests (FITs) are increasingly used to triage screenees for colonoscopy.[3] In September 2016, Hong Kong launched a 2-year FIT-based CRC screening pilot programme for residents aged 61 to 70 years. Each screenee submitted two faecal samples that had been obtained 5 days apart; screenees were referred for diagnostic colonoscopy if at least one of their two-sample FIT values (ie, FIT_2 values) was ≥100 ng/mL. In September 2018, the programme was included in routine management for individuals aged 50 to 75 years to undergo biennial FIT screening.

This study was conducted to characterise the epidemiology of colorectal neoplastic diseases and develop data analytics for the CRC screening programme in Hong Kong. The findings were used to generate epidemiologic insights, parameterise the natural history model of CRC for cost-effective analysis, and infer the presence of advanced neoplasia from FIT_2 values.

Methods

For the natural history model, we stratified screenees by disease stage based on their colonoscopy diagnosis: normal (N), hyperplastic polyps (HP), non-advanced adenoma (NA), serrated lesions (SL), advanced adenoma (AA), colorectal cancer (CRC), and unknown (U). Patients with a classification of unknown were either FIT_2-negative (both FIT_2 values <100 ng/mL) or FIT_2-positive (at least one FIT_2 value ≥100 ng/mL) but had no recorded colonoscopy diagnosis. We assumed that there were two pathways of colorectal neoplastic diseases, namely the conventional adenoma pathway ($N \rightarrow NA \rightarrow AA \rightarrow CRC \rightarrow DC$) and the serrated pathway ($N \rightarrow HP \rightarrow SL \rightarrow CRC \rightarrow DC$); *CRC* and *DC* represent preclinical (undiagnosed) and diagnosed CRC, respectively. The serrated pathway is involved in 10% to 30% of CRC cases.[4]

We developed a sex-specific model with parameters θ and fitted the model to the data by estimating θ using the Markov chain Monte Carlo method. For simplicity, we suppressed the

sex dependence of the model. Let $p(s|a,\theta)$ be the prevalence of disease stage $s\in\{N,HP,NA,SL,AA,CRC\}$ among individuals with age a who have never been diagnosed with CRC. We used the following natural history model to simulate the epidemiology of colorectal neoplastic diseases in a cohort starting at age 20 years in the absence of screening. Without loss of generality, we assumed that the initial cohort size (at age 20 years) was 1. Let $x_s(a)$ be the probability that a particular individual in the cohort had disease stage s at age a, and $\gamma_{s,s'}$ be the progression rate from disease stage s to s'. The natural history model comprised the following differential equations:

$$\frac{dx_N(a)}{da} = -(\gamma_{N,NA}(a) + \gamma_{N,HP}(a) + \mu(a))\, x_N(a)$$

$$\frac{dx_{NA}(a)}{da} = \gamma_{N,NA}\, x_N(a) - \gamma_{NA,AA} x_{NA}(a) - \mu(a) x_{NA}(a)$$

$$\frac{dx_{HP}(a)}{da} = \gamma_{N,HP}\, x_N(a) - \gamma_{HP,SL} x_{HP}(a) - \mu(a) x_{HP}(a)$$

$$\frac{dx_{AA}(a)}{da} = \gamma_{NA,AA} x_{NA}(a) - \gamma_{AA,CRC} x_{AA}(a) - \mu(a) x_{AA}(a)$$

$$\frac{dx_{SL}(a)}{da} = \gamma_{HP,SL} x_{HP}(a) - \gamma_{SL,CRC} x_{SL}(a) - \mu(a) x_{SL}(a)$$

$$\frac{dx_{CRC1}(a)}{da} = \gamma_{AA,CRC1} x_{AA}(a) + \gamma_{SL,CRC1} x_{SL}(a) - \gamma_{CRC1,DC1} x_{CRC1}(a) - \gamma_{CRC1,CRC2} x_{CRC1}(a) - \mu(a) x_{CRC1}(a)$$

$$\frac{dx_{CRC2}(a)}{da} = \gamma_{CRC1,CRC2} x_{CRC1}(a) - \gamma_{CRC2,DC2} x_{CRC2}(a) - \gamma_{CRC2,CRC3} x_{CRC2}(a) - \mu(a) x_{CRC2}(a)$$

$$\frac{dx_{CRC3}(a)}{da} = \gamma_{CRC2,CRC3} x_{CRC2}(a) - \gamma_{CRC3,DC3} x_{CRC3}(a) - \gamma_{CRC3,CRC4} x_{CRC3}(a) - \mu(a)\, x_{CRC3}(a)$$

$$\frac{dx_{CRC4}(a)}{da} = \gamma_{CRC3,CRC4} x_{CRC3}(a) - \gamma_{CRC4,DC4} x_{CRC4}(a) - \mu(a) x_{CRC4}(a)$$

$$\frac{dx_{DCi}(a)}{da} = \gamma_{CRCi,DCi} x_{CRCi}(a) - \gamma_{DCi,Death} x_{DCi}(a) - \mu(a) x_{DCi}(a), \quad i=1,2,3,4$$

where $\mu(a)$ was the non-CRC mortality rate at age a (based on data from the Hong Kong Census and Statistics Department; https://www.censtatd.gov.hk). We inferred the prevalence of each disease stage s at age 20 years ($x_s(20)$) and the progression rates (ie, $\gamma_{s,s'}$) from the screening data. In this cohort simulation, disease prevalence among individuals who had never been diagnosed with CRC was $p(s|a,\theta) = \frac{x_s(a)}{\sum_{s\in W} x_s(a)}$, where $W=\{N,HP,NA,SL,AA,CRC\}$. We assumed that the incidence of CRC diagnosis among screenees would have been identical to the incidence in the general population if no screening had been conducted. We also assumed that if an individual had disease stage s, the probability density function (pdf) of his/her two-sample FIT values, $f(\cdot|s,\theta)$, was independent of age.

Let C_k^+ and C_k^- be the set of screenees in the dataset with and without colonoscopy diagnosis in the k^{th} round of FIT screening, respectively. Because the Hong Kong Cancer Registry (HKCaR) reported cancer data with 5-year age bands, we aggregated cancer incidence for the same age groups in our cohort simulation during formulation of the likelihood function. We used HKCaR 2012-2016 data for statistical inference. Let z_j be the total number of CRC cases in the j^{th} age group during 2012-2016, as recorded by the HKCaR, and λ_j be the probability that an individual would be diagnosed with CRC when he/she was in the j^{th} age group in the cohort simulation. The likelihood function was

$$L(\theta) = \underbrace{\prod_{i\in C_1^+} p(s_{i1}|a_{i1},\theta) f(\boldsymbol{h_{i1}}|s_{i1},\theta)}_{\text{First-time screenees who were FIT}_2\text{-positive and had received a colonoscopy diagnosis } (s_{i1})} \times \underbrace{\prod_{i\in C_2^+} \sum_{s_{i1}\in W} p(s_{i1}|a_{i1},\theta) f(\boldsymbol{h_{i1}}|s_{i1},\theta)\pi(s_{i1},s_{i2},a_{i2}-a_{i1}|a_{i1},\theta) f(\boldsymbol{h_{i2}}|s_{i2},\theta)}_{\text{Repeat screenees who were FIT}_2\text{-positive in the second round of FIT screening and had received a colonoscopy diagnosis } (s_{i2})} \times \underbrace{\prod_{i\in C_2^-} \sum_{s_{i1},s_{i2}\in W} p(s_{i1}|a_{i1},\theta) f(\boldsymbol{h_{i1}}|s_{i1},\theta)\pi(s_{i1},s_{i2},a_{i2}-a_{i1}|a_{i1},\theta) f(\boldsymbol{h_{i2}}|s_{i2},\theta)}_{\text{Repeat screenees who did not receive a colonoscopy diagnosis in either round of FIT screening}} \times \underbrace{\prod_j Poisson(z_j, N\lambda_j)}_{\substack{\text{CRC incidence data from}\\ \text{Hong Kong Cancer Registry}}} \times \underbrace{\prod_j \frac{exp\left(-60\left(max\{0.1-\xi_j,0\}+max\{\xi_j-0.3,0\}\right)\right)}{D}}_{\substack{\text{Prior probability that 10\% to 30\% of CRC cases in each}\\ \text{1-year age group } j \text{ developed via the serrated lesion pathway}}}$$

where ξ_j was the proportion of diagnosed CRC cases that developed via the serrated pathway in the cohort simulation, and the pdf $\frac{\exp(-60(\max\{0.1-\xi_j,0\}+\max\{\xi_j-0.3,0\}))}{D}$ was used to incorporate the prior information that ξ_j should lie between 10% and 30% (D served as the normalisation constant).[4]

For risk prediction analytics, suppose that a screenee at age a_1 had two-sample FIT values $\boldsymbol{h_1}=(h_1^1,h_1^2)$ in the first round of screening, contingent on θ. Thus, the probability that he/she had disease stage s_1 during the first round of screening would be:

$$P(s_1|\boldsymbol{h_1},a_1,\theta) = \frac{p(s_1|a_1,\theta) f(\boldsymbol{h_1}|s_1,\theta)}{\sum_{u\in W} p(u|a_1,\theta) f(\boldsymbol{h_1}|u,\theta)} \quad (1)$$

Additionally, suppose that this screenee was FIT_2-negative in the first round of screening (ie, $\max(\boldsymbol{h_1})<100$ ng/mL and thus not referred for colonoscopy); the probability that he/she had disease stage s at age $a\geq a_1$ would be:

$$P(s|\boldsymbol{h_1},a_1,a,\theta) = \sum_{s_1} P(s_1|\boldsymbol{h_1},a_1,\theta)\pi(s_1,s,a-a_1|a_1,\theta) \quad (2)$$

before he/she underwent the second round of screening. If the screenee returned to the programme for the second round of screening at age a_2, the probability that he/she was FIT_2-positive would be:

$$P(\text{FIT}_2\text{–positivity}|\boldsymbol{h_1},a_1,a_2,\theta) = \sum_s P(s|\boldsymbol{h_1},a_1,a_2,\theta)\int_{max(\boldsymbol{h_2})>100} f(\boldsymbol{h_2}|s,\theta)d\boldsymbol{h_2} \quad (3)$$

If the FIT_2 values in the second round of screening were $\boldsymbol{h_2}$, the probability that the screenee had disease stage s_2 would be updated to:

$$P(s_2|\boldsymbol{h_1},\boldsymbol{h_2},a_1,a_2,\theta) = \frac{P(s_2|\boldsymbol{h_1},a_1,a_2,\theta) f(\boldsymbol{h_2}|s_2,\theta)}{\sum_{u\in W} P(u|\boldsymbol{h_1},a_1,a_2,\theta) f(\boldsymbol{h_2}|u,\theta)} \quad (4)$$

We used the c-statistic to evaluate the predictive power of equations 3 and 4. Specifically, the dataset for equation 3 comprised the FIT_2 values of all repeat screenees, whereas the dataset for equation 4 comprised the disease stages of all repeat screenees who had received a colonoscopy diagnosis.

Results

The complete dataset consisted of screening data from 71 346 men and 91 570 women aged 53 to 77 years who had received FIT screening reports from the Hong Kong Colorectal Cancer Screening Programme by 27 March 2020. Among these participants, 6920 men and 8050 women were repeat screenees who were FIT_2-negative in the first round, returned for a second round of screening after 2 years, and had second-round screening reports.

The fitted model was consistent with the data (Fig 1). We estimated that at age 20 years, >99% of individuals were free of any colorectal polyps or lesions. For both men and women, the annual incidence rate of developing non-advanced adenoma via the conventional adenoma pathway increased between age 20 and 80 years, with median peaks at age 80 years of 9.1% (95% credible interval [CrI]=5.6-13.2%) in men and 9.7% (95% CrI=7.5-12.4%) in women. The age-specific incidence rate of developing hyperplastic polyps via the serrated pathway followed a similar trend, with an earlier peak at age 70 years and a 70% to 75% decrease in magnitude: 2.3% (95% CrI=1.4-3.0%) in men and 3.0% (95% CrI=2.2-3.7%) in women.

The annual progression rates of AA to (undiagnosed) CRC were 5.9% (95% CrI=5.4-6.3%) in men and 6.4% (95% CrI=5.7-7.5%) in women; the corresponding rates of SL to CRC were 3.1% (95% CrI=2.7-3.5%) and 1.9% (95% CrI=1.6-2.3%). The respective mean durations of preclinical stage 1-4 CRC were 2.8, 3.0, 0.58, and 1.0 years in men and 4.2, 1.7, 0.44, and 2.4 years in women. Figure 2 shows the estimated age-specific prevalences in different disease stages in the fitted natural history model.

After adjustments for sampling and measurement errors, we estimated the median maximum FIT_2 value (ie, the determinant for colonoscopy referral) for individuals in each health state. The estimates suggested that FIT_2 values among individuals with SL/AA/CRC are generally lower in

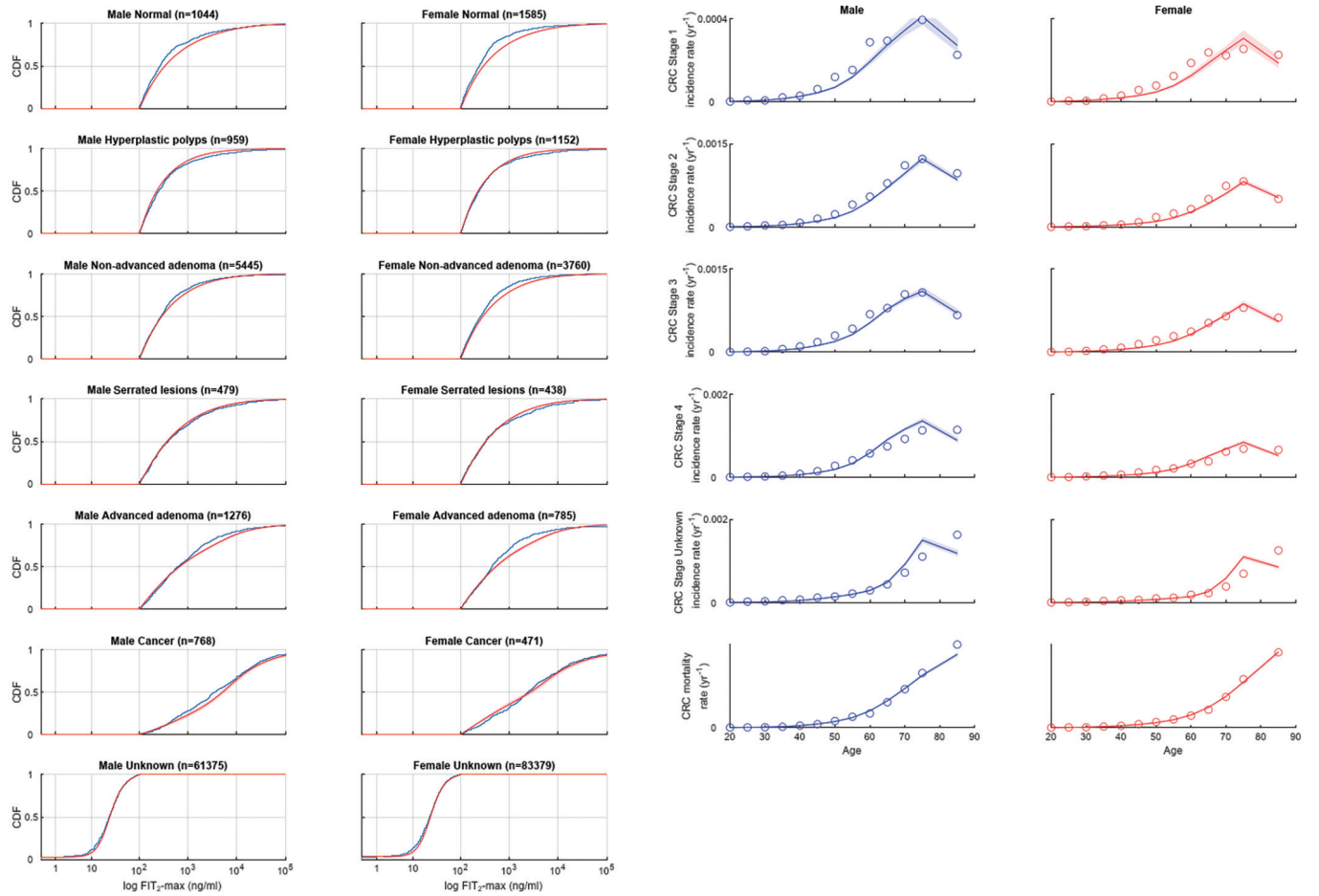

FIG 1. Goodness-of-fit of the fitted model. First two columns show cumulative distribution functions of FIT_2 values, stratified by colonoscopy outcomes. Blue lines represent empirical data, and red lines represent fitted models. Third and fourth columns show age-specific incidence (stratified by stage at diagnosis) and mortality rate of colorectal cancer, respectively. Circles represent empirical data. Lines represent median fitted values. Shaded regions represent corresponding 95% credible intervals.

Abbreviations: CDF, cumulative density function; CRC, colorectal cancer; FIT_2, two-sample faecal immunochemical test.

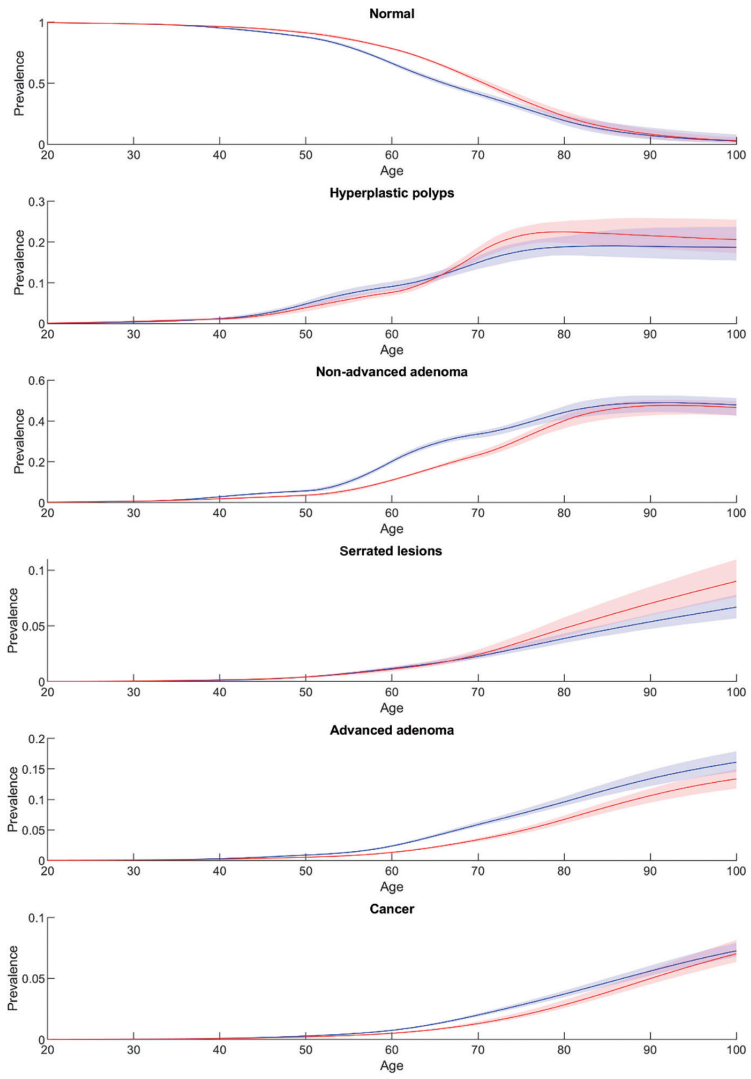

FIG 2. Estimated age-specific prevalences in different disease stages in the fitted natural history model. Blue and red lines represent results for men and women, respectively. Shaded regions represent corresponding 95% credible intervals.

women than in men. Using a positivity threshold of 100 ng/mL for the detection of CRC, we found that FIT_2 had sensitivities of 92% (95% CrI=90-94%) in men and 71% (95% CrI=66-75%) in women; using the same positivity threshold for the detection of SL/AA/CRC, FIT_2 had sensitivities of 58% (95% CrI=56-60%) in men and 47% (95% CrI=45-49%) in women (Fig 3). For the detection of CRC or SL/AA/CRC, FIT_2 had specificities of approximately 85% in men and 90% in women.

To assess the predictive power of equations 3 and 4, we used a dataset consisting of 6920 male and 8050 female repeat screenees. Among them, 12.2% and 8.2% were FIT_2-positive and had been referred for colonoscopy. The corresponding percentages predicted by equation 3 (which projected disease progression for approximately 2 years, based on the probability distribution of disease stages inferred from first-round FIT_2 values) were 16.2% and 11.8%. The c-statistics of equation 3 for predicting second-round FIT_2 positivity among repeat screenees, based on their first-round FIT_2 values, were 0.52 (95% CrI=0.51-0.54) for men and 0.5 (95% CrI=0.48-0.52) for women. These results indicate that equation 3 had very limited predictive power in predicting FIT_2 positivity among repeat screenees at the individual level.

The repeat screenees included 750 men and 582 women who were FIT_2-positive in second-round screening and had colonoscopy results. Among them, 2.9% of men and 2.2% of women had been diagnosed with CRC; 19.0% of men and 15.6% of women had been diagnosed with advanced colorectal diseases (SL/AA/CRC). The corresponding percentages predicted by equation 4 were 2.3% and 2.5% for CRC and 15.3% and 13.5% for advanced colorectal diseases. The c-statistics of equation 4 for predicting CRC from both-round FIT_2 values were 0.73 (95% CrI=0.57-0.84) for men and 0.83 (95% CrI=0.67-0.92) for women. The c-statistics of equation 4 for predicting SL/AA/CRC were 0.61 (95% CrI=0.55-0.66) for men and 0.60 (95% CrI=0.53-0.66) for women. These results indicate that equation 4 had moderate power in predicting advanced colorectal diseases from both rounds of FIT_2 values (based on the fitted natural history model).

Discussion

In Hong Kong, biennial FIT screening has been included in routine management for individuals aged 50 to 75 years. We developed new analytics to characterise the epidemiology and natural history of CRC in Hong Kong. The findings may help to optimise the CRC screening programme.

First, the current CRC screening programme uses a uniform threshold for FIT positivity, regardless of age and sex. Our fitted model showed that FIT values among individuals diagnosed with advanced colorectal diseases were generally lower in women than in men. This finding suggests that the use of sex-specific FIT positivity thresholds, which have been implemented in the CRC screening programme in Stockholm-Gotland (Sweden),[5] would allow comparable test performance (sensitivity and specificity) for the detection of colorectal neoplastic diseases.

Second, our fitted model had moderate power in predicting advanced colorectal neoplastic diseases from FIT values (before colonoscopy), but it had limited power in predicting FIT positivity among repeat screenees. Studies such as the Asia-Pacific Colorectal Screening scoring system have shown that factors such as family history of CRC (in first-degree relatives), smoking history, and body mass index may provide good predictive power for

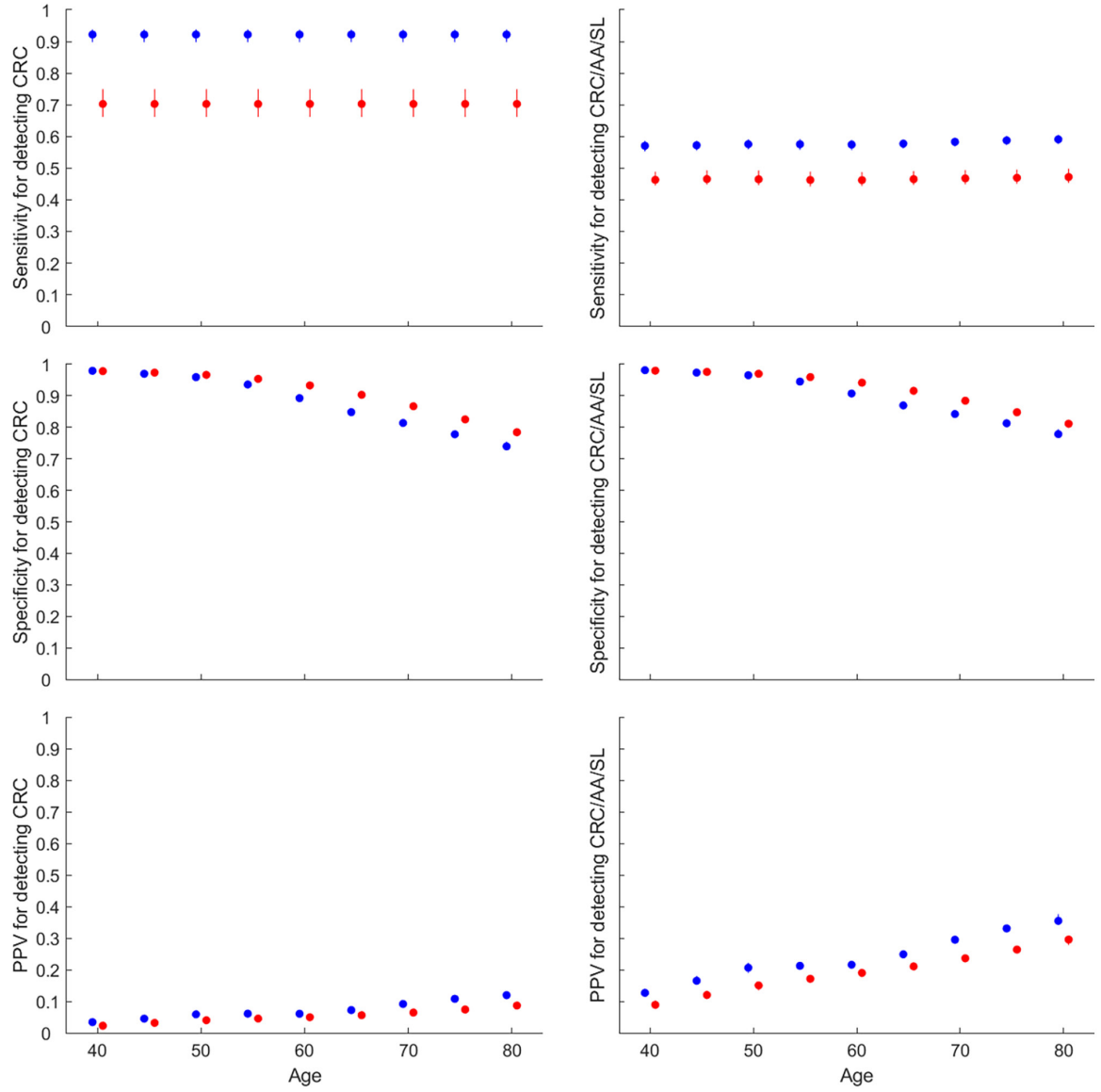

FIG 3. Predictive model performance. Blue and red dots represent results for men and women, respectively. Error bars represent corresponding 95% credible intervals.
Abbreviations: AA, advanced adenoma; CRC, colorectal cancer; PPV, positive predictive value; SL, serrated lesions.

advanced neoplasia. Although these data should be readily available in screenees' electronic health records, they are not currently available in the Hong Kong CRC screening programme database and thus could not be included as risk factors in our model. We recommend linking the screening database to screenees' electronic health records to ensure that data regarding CRC risk factors can be accessed to optimise analytics for prediction of advanced neoplasia. The incorporation of risk estimates for individual screenees could also facilitate the development of personalised screening algorithms. For example, screenees with a higher risk of neoplasia may require more frequent screening, whereas individuals with a lower risk of neoplasia may undergo less frequent screening (eg, after consecutive negative FITs).

Third, routine data from FIT screening programmes can be readily used to characterise CRC epidemiology. Our fitted natural history model provides an evidence-based analytical platform for future optimisation of the CRC screening programme. The cost-effectiveness of potential alternative screening algorithms, such as sex-specific FIT positivity thresholds and differences in age range and screening frequency, should be evaluated

by including economic components of healthcare (eg, cost of screening and treatments) in current mathematical simulation models. This type of mechanism has been used to inform CRC screening strategies in other countries such as Australia and the United States.[6,7]

Fourth, participation and compliance with recommended guidelines are important factors for the success of a screening programme. Policymakers should monitor participation and compliance rates, with the goal of providing additional support to underserved populations. Proactive and strategic invitations may help unscreened individuals to engage with the screening programme. The screening process could be optimised by combining the screening database and the centralised electronic health record system.

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Screening interval for diabetic retinopathy: a personalised approach (abridged secondary publication)

J Lian *, CLK Lam, TQ Thach, S McGhee, CSC Fung, ASK Kwong, CKV Chau, JCH Chan

KEY MESSAGES

1. A Hong Kong–specific algorithm with good discriminatory and calibration powers was developed to identify individuals with diabetes who have a high risk of sight-threatening diabetic retinopathy (STDR), compared with individuals with diabetes who have a lower risk of STDR.
2. Overall, the use of a risk-based interval is safe; it can prevent blindness, increase the preservation of sight years relative to annual screening, and reduce the frequency of screening among individuals with diabetes who have a lower risk of STDR.

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Introduction

Diabetic retinopathy (DR) is among the most common microvascular complications of diabetes mellitus (DM) and the leading cause of new cases of blindness in developed countries. DR screening is a cost-effective approach to prevent blindness. However, the optimal screening interval remains controversial. In 2010, Hong Kong began systematic DR screening as a component of the multi-disciplinary risk assessment and management programme for diabetes (RAMP-DM). The Iceland model was used to determine screening intervals according to individualised risk of sight-threatening diabetic retinopathy (STDR).[1] However, the Iceland model significantly underestimated the risk of STDR in our pilot DR screening study, although it has an acceptable discrimination level. Risk factors for DR were mainly based on western diabetic populations. Using data collected during the screening programme in Hong Kong, we sought to identify the most important risk factors and improve risk stratification for Hong Kong populations. In this study, we aimed to (1) develop an STDR prediction model based on the diabetic population in Hong Kong, using data from the systematic DR screening programme; (2) test the internal validity of the resulting model; (3) investigate the safety, feasibility, and cost-effectiveness of the prediction model; and (4) build a cost-effectiveness model that could estimate the cost-effectiveness of the new prediction model.

Methods

This retrospective cohort study was conducted to develop an algorithm to predict the risk of STDR in Hong Kong populations. Individuals who participated in RAMP-DM on or before 31 December 2016 and had at least one DR screening assessment using the standardised grading were eligible for inclusion. DR was graded as no DR (R0), background DR (R1), pre-proliferative DR (R2), or proliferative DR (R3) / maculopathy (M1) according to the UK national DR screening programme procedures. The DR grading R2 and R3/M1 were regarded as STDR. The risk algorithm was developed using data from individuals without STDR (ie, individuals with a DR grading of R0 or R1) at baseline who had at least one follow-up record. Eligible individuals were randomly allocated into derivation and validation datasets at a ratio of 2:1.

Parametric survival analysis using the Weibull distribution provided the best fit for the risk algorithm after stratification according to sex and DR grading of R1 at baseline (ie, R0 male, R0 female, R1 male, and R1 female groups). Time from baseline screening was used as the time scale (t), and the first occurrence of STDR after baseline screening was regarded as the outcome event. Both right censoring and interval censoring were considered in the model.

Potential predictors were identified through literature review; they were at least 80% complete

in the RAMP-DM data. Best-fitting predictors were selected using a recommended procedure for prognostic survival modelling. Univariate analysis was conducted to select significant variables, which were then entered into a multivariate model; subsequently, the Wald test was used to reduce the number of covariates. Selections were confirmed using the Akaike information criterion. Previously excluded variables were re-entered into the model to ensure that none would improve prediction results. A separate risk algorithm was derived for each of the four groups: R0 male, R0 female, R1 male, and R1 female.

Coefficients from the survival model were transformed into a mathematical algorithm and applied to the validation cohort. Algorithm performance was assessed by comparing the total number of STDR events over 2 years (ie, 2-year observed risk) with the 2-year predicted risk, then examining discriminatory power using receiver operating characteristic curves and calibration power using the Hosmer-Lemeshow Chi-squared test.

The algorithm was then used to estimate the time for an individual to reach a pre-determined STDR risk margin. The time was converted to screening intervals of 6 months (for predictions of ≤9 months), 12 months (for predictions between 10 and 21 months), or 24 months (for predictions of ≥22 months), based on current practice. To assess the safety of the risk-based intervals, we compared the observed time for detection of new STDR cases with the assigned intervals.

An individual-based Markov state-transition model was constructed to simulate the long-term effect on cost and the consequences of using risk-based screening intervals established by the Hong Kong algorithm, compared with a fixed annual screening strategy. The model simulated transitions among health states based on the natural progression of DR (R0, R1, R2, or R3) and maculopathy, blindness, and death over an individual's lifetime. Values for model parameters (eg, transition probabilities and costs) were based on data from Hong Kong when possible. If no data from Hong Kong were available, international data were used, with adjustment to fit local circumstances. If no international or local data were available, expert opinions were used as a basis for model parameters. In total, 100 000 individuals, with profiles randomly selected from the RAMP-DM cohort, were modelled for each screening strategy. The mean lifetime cost and consequences in term of blindness incidence, number of sight years preserved, and quality-adjusted life-years (QALYs) were summarised and compared. The procedure was repeated 10 times; the mean costs and effectiveness results were used to generate incremental cost-effectiveness ratios. The provider perspective was adopted for the base case analysis.

Results

Six predictors were selected in the final best-fit model: duration of diabetes, HbA1c level, systolic blood pressure, presence of chronic kidney disease (defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 or urinary albumin to creatinine ratio ≥3 mg/mmol),[3] use of DM medication, and age. Prediction performance validation revealed that the respective 2-year predicted and observed risks were 5.6% and 5.1% (P=0.724) for men and 4.8% and 4.6% (P=0.099) for women. The discriminatory powers of the prediction models were moderate to good, with a receiver operating characteristic curve of 0.797 (95% confidence interval=0.780-0.814) for men and 0.810 (95% confidence interval=0.793-0.827) for women.

Using a risk margin of 2.5% for both R0 and R1 (ie, 2.5%/2.5%), which was approximately equivalent to the overall annual incidence of STDR, 96.6% (1107/1146) of STDR cases would have been assigned to a safe screening interval near the time of STDR development, whereas 3.0% (34/1146) of STDR cases would have had a screening date 12 months beyond the time of STDR development. None of these 34 cases were R3 requiring urgent referral, and 70% were due to M1. Using this risk margin, 36.6%, 8.5%, and 54.8% of subjects would have been assigned to 6-month, 12-month, and 24-month screening intervals, respectively, leading to a 9.2% increase in the total number of screening visits over a 2-year period. Using risk margins of 2.5% for R0 and 5.0% for R1 (approximately equivalent to the annual incidence in the R1 group), 93.5% of STDR cases would have been assigned to a safe screening interval, but 4.1% of STDR cases would have had a 12-month delay in detection; notably, none of these cases were R3. Approximately 26.7%, 14.5%, and 58.8% of subjects would have been assigned to 6-month, 12-month, and 24-month screening intervals, leading to a 2.7% decrease in the total number of screening visits.

The use of a risk-based screening with a risk margin of 2.5% for both R0 and R1 led to a mean decrease of -0.32% in the cumulative incidence of blindness, which would preserve approximately 0.015 sight years per individual according to the model; however, it would have a limited effect on the number of QALYs (approximately 0.0003 QALYs gained per person), compared with annual screening. This approach also carried an additional lifetime cost of HK$316 per individual, compared with annual screening. Overall, the risk-based screening strategy would cost HK$99 990 per additional case of blindness prevented and HK$20 752 per additional sight year preserved, compared with annual screening. Because the number of QALYs did not substantially differ between risk-based screening

and annual screening, the calculation of incremental cost-effectiveness ratio according to QALYs had limited use. Risk margins of 2.5% for R0 and 5.0% for R1 led to a mean decrease of -0.20% in the cumulative incidence of blindness, 0.006 sight years preserved per person, 0.001 QALYs gained per person, and an increased lifetime cost of HK$162 per individual, compared with annual screening.

Discussion

Our prediction model generally demonstrated good discriminatory and calibration powers when the predicted and observed risks of STDR were compared. Most STDR cases would be assigned to a safe screening interval around the time of STDR development. The use of a higher risk margin would reduce safety but would require fewer screening visits.

Risk-based screening using a risk margin of 2.5% for both R0 and R1 prevented blindness and preserved sight years. The proportion of blindness prevention was 0.32%, which represented vision preservation in an additional 320 of every 100 000 individuals with diabetes. Annual screening is already an effective screening strategy; the additional benefit of the risk-based screening mainly arises from assigning high-risk individuals to semi-annual screening, rather than annual screening.

There is no benchmark for an acceptable threshold value for prevention of a case of blindness or saving of a sight year. Vision loss can lead to comorbidities including falls and depression.[4] These comorbidities can result in further use of public healthcare resources, primarily by older people with chronic diseases such as diabetes. The benefit of avoiding blindness was not considered in the current cost-effectiveness analysis. In this study, we used a conservative approach from a government perspective when estimating the cost per case of blindness prevented or sight year preserved.

A risk-based approach with individualised screening intervals improves vertical equity, which is defined as subjects with different levels of needs (ill health) have appropriately different access to healthcare services. In contrast, fixed annual screening provides the same screening interval for the entire population, regardless of risk. The use of different risk margins involve trade-off between screening interval safety and resource utilisation during screening. If there are sufficient resources to accommodate additional screening visits, an approach involving a risk margin of 2.5% for both R0 and R1 is the safest strategy.

Conclusion

A Hong Kong–specific algorithm with good discriminatory and calibration powers was developed to identify individuals with diabetes who have a high risk of STDR. Overall, the use of a risk-based interval is safe and reduces the need for more frequent screening of low-risk individuals. However, more research is needed to refine the risk for the higher risk people so that fewer of these cases need to be allocated to a 6-monthly screening interval.

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Weight loss versus continuous positive airway pressure therapy for obstructive sleep apnoea on metabolic profile stratified by craniofacial restriction: abridged secondary publication

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KEY MESSAGES

1. Weight loss by lifestyle modification programme (LMP) achieved more reduction in subclinical inflammation than continuous positive airway pressure (CPAP) therapy at 6 months among obese patients with moderate to severe obstructive sleep apnoea (OSA).
2. Weight loss by LMP improved insulin sensitivity better than CPAP therapy at 6 months among obese patients with moderate to severe OSA, with smaller proportion of patients having abnormal glucose regulations by 6 months (46.1% vs 63.6%).
3. Baseline sleep apnoea severity was associated with neck circumference, mandibular length, maxillary angle, and mandibular angle.
4. Changes of subclinical inflammation and insulin sensitivity were not significantly different between patients with different degrees of craniofacial restriction.
5. Only weight loss was associated with the percentage change of apnoea-hypopnoea index at 6 months.

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Introduction

Obstructive sleep apnoea (OSA) is characterised by repetitive episodes of upper airway obstruction causing intermittent hypoxia and arousals, leading to systemic inflammation, insulin resistance, dyslipidaemia, hypertension, and cardiovascular consequences.[1] Subclinical inflammation as evidenced by elevated C-reactive protein (CRP) suggests the mechanism of increased atherosclerosis in patients with OSA. Continuous positive airway pressure (CPAP) is the first-line treatment for OSA, as it is effective in improving airway patency and the apnoea-hypopnoea index (AHI), resulting in reduced daytime sleepiness. However, wide variance (25% to 75%) in adherence may affect the effectiveness of CPAP therapy. Moreover, CPAP therapy alone does not result in improvement in visceral adiposity, insulin resistance, or metabolic dysfunction.

Obesity is a major risk factor for OSA. Weight reduction for overweight patients with OSA may improve cardiometabolic abnormalities, which are often associated with OSA. However, the chance of cure (AHI of <5 events/hr) remains low, despite substantial improvement of OSA symptoms after various weight loss programmes. Apart from obesity, craniofacial restriction is another risk factor, especially among Chinese populations. A smaller craniofacial skeletal size as determined by maxillomandibular volume (MMV) indicates more craniofacial restriction; patients with more craniofacial restriction can achieve greater benefits from weight loss.[2] Therefore, craniofacial structure is a potential predictor of effectiveness of weight loss for OSA improvement.

We hypothesised that weight loss in patients with more craniofacial restriction would result in better improvement in metabolic profile than those with less craniofacial restriction or those treated with CPAP. We compared the effect of weight loss or CPAP alone on subclinical inflammation and insulin sensitivity in obese patients with moderate to severe OSA stratified according to craniofacial restriction.

Methods

A total of 363 obese patients (body mass index [BMI], ≥25 kg/m^2) with clinical suspicion of OSA were recruited from the respiratory clinic at the Prince of Wales Hospital between 15 September 2017 and 28 January 2020. Patients underwent a home sleep study with the Embletta device, which had been validated against polysomnography in Hong Kong Chinese population.[3] Patients with AHI of ≥15/hr on home sleep study received home autoCPAP titration.

Patients with baseline blood level of high-sensitivity CRP (hsCRP) of ≥1 mg/L were randomly assigned to receive either lifestyle modification programme (LMP) or CPAP therapy for 6 months. Patients in the LMP group received dietary consultation weekly in the first 4 months, and monthly in the following 2 months. A caloric reduction of 10% to 20% in daily energy intake was set as a goal, which was adjusted based on changes in body weight with target BMI towards 23 kg/m^2. Patients were encouraged to see an exercise instructor at least once and perform 30-minute aerobic exercise two to three times a week. Patients in the CPAP group started an auto CPAP therapy nightly during the study period.

Patients were assessed at baseline and 6 months by the Epworth Sleepiness Scale (ESS), three-dimensional computed tomography of the head/neck region to evaluate the MMV for craniofacial restriction, test for serum levels of hsCRP, and oral glucose tolerance test for insulin sensitivity. Home sleep study was repeated at 6 months.

Results

A total of 194 obese patients with moderate to severe OSA were randomly assigned to receive either LMP (n=128) or CPAP therapy (n=66). At baseline, the LMP group had lower insulin resistance and fasting plasma insulin, shorter upper face height, and larger maxillary angle than the CPAP group (Table 1). Baseline AHI was correlated with insulin sensitivity as reflected by the Matsuda index (rho= -0.24, P=0.001) but not hsCRP. Following 6 months of intervention, the LMP group achieved significant improvement in body weight, ESS, AHI, hsCRP, Matsuda index, and insulin resistance, which was reflected by the homeostatic model assessment for insulin resistance (HOMA-IR). The CPAP group also achieved significant improvement in ESS, AHI, and HOMA-IR, but not hsCRP or insulin sensitivity. The objective CPAP usage was 4.02±2.0 hours, with 95th centile pressures at 12.7±1.7 cm H_2O and the residual AHI of 3.5±1.8 events/hr. The LMP group achieved greater improvement in AHI, hsCRP, and insulin sensitivity than the CPAP group did (Table 2). Significantly smaller proportion of patients having abnormal glucose regulations at 6 months in the LMP group than in the CPAP group (46.1% vs 63.6%, P=0.02).

For the radiological parameters, AHI was correlated with mandibular angle (r= -0.2, P=0.005) but not MMV. Regression analysis showed that AHI was associated with neck circumference (beta=3.63, P<0.001), ESS (beta=0.598, P=0.031), mandibular length (beta= -5.9, P=0.013), maxillary angle (beta=0.763, P=0.044), and mandibular angle (beta= -1.282, P=0.006). Patients in the LMP group were subdivided according to the mean MMV of 229.6 cm^3 into the small MMV group (n=58) and the large MMV group (n=70). Results of the two subgroups were similar with those of the overall LMP group (Table 3). More patients in the small MMV group than in the large MMV group achieved improvement in glucose regulations (41.4% vs 24.3%, P=0.024). Multivariate analysis showed that only weight loss was associated with the percentage change of AHI in 6 months (beta= -1.114, 95% confidence interval= -2.194 to -0.033, P=0.043).

Discussion

For obese patients with moderate to severe OSA, LMP was more effective to reduce AHI and body weight and improve subclinical inflammation (absolute change of hsCRP= -0.7 mg/L, -30.4% from baseline) and insulin sensitivity (absolute change of 0.6 in Matsuda index, 25.8% from baseline) than CPAP therapy. Patients in the CPAP group showed modest improvement in HOMA-IR at 6 months but not in hsCRP or insulin sensitivity. Insulin sensitivity improved significantly greater in the LMP group than in the CPAP group (0.6 vs 0.0, P<0.001). The difference in the response in HOMA-IR and the Matsuda index highlights the variability of the two evaluation tools, as the Matsuda index uses data from oral glucose tolerance test and is more accurate than HOMA-IR, which is a steady state measurement.

We have previously shown that therapeutic CPAP versus subtherapeutic CPAP at 4 cm H_2O over 6 months did not significantly reduce visceral fat thickness, levels of adipokines and severity of fatty liver. On contrary, LMP could reduce the severity of OSA and daytime sleepiness among obese Chinese patients with moderate and severe OSA. In a study of obese patients (BMI, 38.1 kg/m^2) with moderate to severe OSA who were randomised to receive CPAP (lost 0.7 kg), weight loss programme (lost 6.9 kg), or combination intervention (lost 7.1 kg), there were reduction in hsCRP (-7.24% in CPAP group, -31.4% in weight loss group, and -26.73% in combination intervention) and improvement in insulin sensitivity (0.05 vs 0.63 vs 0.44 $\times 10^{-4}$/min^{-1}/μU/mL) in the weight loss group and combination intervention group but not in the CPAP group.[4] Weight loss is superior to CPAP therapy in improving subclinical inflammation and glycaemic control. Weight-loss intervention or lifestyle modification should thus be emphasised, although CPAP therapy is still important in patients with excessive daytime sleepiness, high blood pressure or cardiovascular risk, and low BMI. Further research should focus on the cost-effectiveness of various weight loss programmes in terms of metabolic and cardiovascular outcomes among patients with sleep apnoea.

Craniofacial restriction is a risk factor for OSA, as it affects the pharyngeal airway space, especially in Chinese populations. For the same degree of obesity, Chinese patients have more severe OSA and more

TABLE 1. Baseline characteristics of patients in the lifestyle modification programme (LMP) group and the continuous positive airway pressure (CPAP) group

Variable	All (n=194)	LMP group (n=128)	CPAP group (n=66)
Age, y	50.8±10.4	50.8±10.4	50.8±10.5
Male	129 (66.5)	85 (66.4)	44 (66.7)
Weight, kg	81.4 (74-92)	81 (74-94)	83.8 (74.1-91.3)
Body mass index, kg/m^2	29.7 (27.3-32.5)	29.6 (27.4-32.5)	29.7 (27.1-32.5)
Neck circumference, cm	40±3.3	39.8±3.3	40.3±3.2
Waist circumference, cm	104±9.6	103.9±10.0	104.1±8.9
Hip circumference, cm	107.7±8.1	107.7±8.0	107.6±8.3
Waist-to-hip ratio	0.97±0.06	0.96±0.06	0.97±0.06
Smoking status			
Never	137 (70.6)	85 (66.4)	52 (78.8)
Quitted	22 (11.3)	16 (12.5)	6 (9.1)
Current	35 (18)	27 (21.1)	7 (12.1)
Physical active (counts)	86 (44.3)	55 (44)	31 (47)
Cardiometabolic illness			
Hypertension	114 (58)	78 (60.9)	36 (54.5)
Ischaemic heart disease	6 (3.1)	5 (3.9)	1 (1.5)
Known diabetes mellitus	6 (3.1)	3 (2.3)	3 (4.5)
Abnormal glucose regulation	120 (61.9)	78 (60.9)	41 (63.6)
Cerebrovascular accident	3 (1.5)	1 (0.8)	2 (3)
Inflammatory and metabolic parameter			
High-sensitivity C-reactive protein, mg/L	2.4 (1.6-4.3)	2.4 (1.6-4.3)	2.4 (1.5-4.3)
Matsuda index	2.2 (1.5-3.1)	2.3 (1.5-3.5)	2.2 (1.3-3.0)
Homeostatic model assessment for insulin resistance	3.3 (2.1-4.9)	3.1 (2.0-4.7)	3.9 (2.6-5.3)†
Plasma glucose at 0 min	95.5 (88.3 -104.5)	95.5 (88.3-102.7)	99.1 (91.9-107.1)
Plasma glucose at 30 min	182.3 (162.2-203.6)	176.6 (161.3-202.7)	184.7 (167.6-203.6)
Plasma glucose at 60 min	196.4 (162.2-199.1)	201.8 (163.1-238.7)	196.4 (157.7-231.1)
Plasma glucose at 120 min	144.1 (118.9-189.2)	145.9 (113.5-186.5)	143.2 (126.1-200.5)
Plasma insulin at 0 min	13.6 (9-20.7)	13.1 (8.4-20.1)	15.7 (10.5-21.2)†
Plasma insulin at 30 min	82.8 (52.6-145.5)	78.3 (52.1-145.9)	102.3 (55.3-146.9)
Plasma insulin at 60 min	111.4 (66.6-168.1)	111.8 (66.7-164.1)	108.1 (66.7-178.9)
Plasma insulin at 120 min	92.5 (58.7-159)	88.6 (56.1-149.5)	96.1 (58.6-195.7)
Sleep parameter			
Epworth Sleepiness Scale	11.5±5.4	11.7±5.4	10.7±5.1
Apnoea-hypopnoea index (AHI), events/hr	44.1 (26.4-62.8)	44.1 (26.3-61.1)	43.6 (29.3-71.4)
AHI (supine), events/hr	57±23.2	55.4±23.2	57.8±23.5
AHI (non-supine), events/hr	25.6 (15.2-46.5)	25.3 (14.0-44.8)	29.2 (16.7-49.8)
Minimal oxygen saturation, %	72.6±9.4	73.6±9.2	71.0±9.0
Oxygen desaturation index 3, /hr	42.1 (25.8-59.7)	42 (25.9-57.6)	44.1 (26.5-64.8)
% of total recording time of oxygen saturation <90%	8.8 (3.2 -27.7)	8.7 (2.9-24.4)	10.8 (4.4-34.2)
Radiological parameter			
Maxillomandibular volume, cm^3	229.6±37.6	231.5±36.2	227.4±38.1
Upper face height, cm	5.5±0.6	5.5±0.6	5.7±0.5*
Lower face height, cm	6.9±0.7	6.9±0.7	6.8±0.7
Total face height, cm	12.3±0.9	12.2±0.9	12.3±0.8
Maxillary length, cm	9.8±0.5	9.8±0.5	9.8±0.7
Mandibular length, cm	8.5 (8.1-8.9)	8.6 (8.1-9.0)	8.5 (8.2-8.8)
Maxillary angle, degree	71.2 (68.6-74.8)	72.2 (69.2-75.1)	70.7 (67.2-72.8)†
Mandibular angle, degree	63.1 (60.6-65.6)	63.4 (60.9-65.9)	62.8 (60.2-64.9)

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

† P<0.05 between LMP group and CPAP group

TABLE 2. Change in body weight, sleep apnoea severity, inflammatory and metabolic parameters between the lifestyle modification programme (LMP) group and the continuous positive airway pressure (CPAP) group

Variable	LMP group (n=128)*	CPAP group (n=66)*	P value†
Body weight, kg	-4.7 (-8.2 to -2.3)	0.7 (-1.2 to 2.3)	<0.001
Body mass index, kg/m²	-1.8 (-2.9 to -0.8)	0.3 (-0.4 to 0.9)	<0.001
Epworth Sleepiness Scale	-4.2±5.4	-3.1±4.6	0.15
Apnoea-hypopnoea index (AHI), events/hr	-11.0 (-19.0 to -2.0)	-2.7 (-14.2 to 5.8)	0.02
AHI (supine), events/hr	-8.0 (-17.6 to 0.1)	-0.1 (-9.1 to 8.1)	<0.001
AHI (non-supine), events/hr	-6.9 (-20.1 to 1.7)	-2.0 (-17.7 to 12.4)	0.104
Minimal oxygen saturation, %	1.5 (-2.0 to 6.0)	5.0 (1.0 to 8.0)	0.005
Oxygen desaturation index 3, %	-10.9 (-18.3 to -2.3)	-5.0 (-19.8 to 5.5)	0.119
% of total recording time of oxygen saturation <90%	-1.3 (-8.8 to 1.2)	-3.8 (-15.5 to -0.7)	0.015
High-sensitivity C-reactive protein, mg/L	-0.7 (-1.4 to -0.0)	-0.3 (-0.9 to 0.4)	0.012
Matsuda index	0.6 (0.0 to 1.9)	0.0 (-0.5 to 0.5)	<0.001
Homeostatic model assessment for insulin resistance	-0.5 (-1.9 to 0.3)	-0.4 (-1.8 to 0.4)	0.42
Plasma glucose at 0 min, mg/dL	-2.7 (-10.8 to 0.0)	-0.9 (-4.1 to 3.6)	0.020
Plasma glucose at 30 min, mg/dL	-9.0 (-27.0 to 7.2)	-0.9 (-16.7 to 14.4)	0.015
Plasma glucose at 60 min, mg/dL	-23.4 (-43.2 to 0.9)	2.7 (-9.5 to 21.6)	<0.001
Plasma glucose at 120 min, mg/dL	-16.2 (-43.2 to 7.2)	-3.6 (-29.3 -14.4)	0.087
Plasma insulin at 0 min, μU/mL	-1.7 (-7.2 to 1.4)	-1.4 (-6.0 to 1.6)	0.39
Plasma insulin at 30 min, μU/mL	-11.7 (-35.5 to 7.4)	-3.7 (-36.5 to 30.1)	0.13
Plasma insulin at 60 min, μU/mL	-26.4 (-52.4 to 0.9)	1.7 (-10.0 to 39.0)	<0.001
Plasma insulin at 120 min, μU/mL	-19.4 (-62.8 to 7.2)	6.5 (-35.5 to 42.4)	0.001

* Data are presented as mean±standard deviation or median (interquartile range)
† Adjusted mean differences were computed from analysis of covariance model by adjusting baseline values

TABLE 3. Change in body weight, sleep apnoea severity, inflammatory and metabolic parameters among the small and large maxillomandibular volume (MMV) subgroups of the lifestyle modification programme (LMP) group and the continuous positive airway pressure (CPAP) group

Variable	LMP group		CPAP group (n=66)*	P value
	Small MMV group (n=58)*	Large MMV group (n=70)*		
Body weight, kg	-4.3 (-6.4 to -2.0)	-5.6 (-9.3 to -2.6)	0.7 (-1.2 to 2.3)	<0.001†‡
Body mass index, kg/m²	-1.7 (-2.4 to -0.7)	-1.9 (-3.1 to -0.9)	0.3 (-0.4 to 0.9)	<0.001†‡
Epworth Sleepiness Scale	-4.3±5.2	-4.2±5.6	-3.1±4.6	0.35
Apnoea-hypopnoea index (AHI), events/hr	-10.3 (-19.4 to -2.1)	-11.6 (-18.9 to 0.0)	-2.7 (-14.2 to 5.8)	0.067
AHI (supine), events/hr	-7.8 (-17.3 to 1.8)	-10.6 (-19.0 to 0.0)	-0.1 (-9.1 to 8.1)	0.002†‡
AHI (non-supine), events/hr	-6.3 (-19.3 to -0.1)	-9.4 (-24.0 to 3.8)	-2.0 (-17.7 to 12.4)	0.223
Minimal oxygen saturation, %	1.5 (-2.0 to 6.0)	1.5 (-2.0 to 7.0)	5.0 (1.0 to 8.0)	0.016‡
Oxygen desaturation index 3, %	-10.2 (-17.2 to -1.5)	-11.6 (-20.3 to -3.3)	-5.0 (-19.8 to 5.5)	0.239
% of total recording time of oxygen saturation <90%	-1.3 (-7.2 to 1.3)	-1.4 (-11.9 to 1.1)	-3.8 (-15.5 to -0.7)	0.045
High-sensitivity C-reactive protein, mg/L	-0.7 (-1.35 to -0.1)	-0.7 (-1.4 to 0.0)	-0.3 (-0.9 to 0.4)	0.039†
Matsuda index	0.5 (-0.3 to 1.9)	0.6 (0.1 to 2.0)	0.0 (-0.5 to 0.5)	<0.001†‡
Homeostatic model assessment for insulin resistance	-0.6 (-1.6 to 0.2)	-0.4 (-2.4 to 0.3)	-0.4 (-1.8 to 0.4)	0.712
Plasma glucose at 0 min	-5.4 (-10.9 to 1.8)	-1.8 (-7.7 to 0.0)	-0.9 (-4.1 to 3.6)	0.048
Plasma glucose at 30 min	-11.7 (-27.0 to 7.2)	-9.0 (-27.0 to 7.2)	-0.9 (-16.7 to 14.4)	0.052
Plasma glucose at 60 min	-16.2 (-43.2 to 7.7)	-23.4 (-43.2 to 1.8)	2.7 (-9.5 to 21.6)	<0.001†‡
Plasma glucose at 120 min	-12.6 (-45.9 to 11.3)	-19.8 (-37.8 to 3.6)	-3.6 (-29.3 -14.4)	0.219
Plasma insulin at 0 min	-1.7 (-6.4 to 1.3)	-1.8 (-8.1 to 2.1)	-1.4 (-6.0 to 1.6)	0.674
Plasma insulin at 30 min	-4.6 (-25.1 -17.4)	-14.8 (-45.6 -0.0)	-3.7 (-36.5 to 30.1)	0.029
Plasma insulin at 60 min	-21.3 (-43.4 to 12.7)	-30.4 (-71.6 - -2.3)	1.7 (-10.0 to 39.0)	<0.001†‡
Plasma insulin at 120 min	-19.4 (-64.2 to 9.5)	-19.0 (-60.7 to 1.3)	6.5 (-35.5 to 42.4)	0.005†‡

* Data are presented as mean±standard deviation or median (interquartile range)
† P<0.05 between small MMV group and CPAP group
‡ P<0.05 between large MMV group and CPAP group

craniofacial restriction than Caucasians.[5] In a study evaluating MMV of 52 obese (BMI, 34±2.7 kg/m^2) male Caucasians with moderate to severe OSA (AHI, 42.9±21.3 /hr), improvement in OSA was more evident in those with a smaller craniofacial skeleton after 6 months of weight loss programme.[2] In the present study, patients with small MMV and large MMV were comparable in terms of percentage change in AHI. This suggests complex interaction of upper airway anatomy and OSA. There was no true inferior bony border in the evaluation of the MMV and no consideration of the curvature/angles of maxilla and mandible, which play significant role in previous craniofacial studies involving OSA. Moreover, ethnicity affects the definition of craniofacial restriction; more research in this area with international collaborations is warranted.

In the present study, a validated home sleep study was used, which underestimated the true severity of OSA because the recording time was used as the denominator in calculating AHI. The CPAP group had significant improvement in sleep apnoea severity at 6 months than at baseline and better improvement in minimal oxygen saturation at 6 months than the LMP group. Actigraphic measurement should have added in the home sleep study to eliminate underestimation. One previous study reported considerable night-to-night variability of OSA, with differences in oxygen desaturation index of >10/hr between nights among 84.4% and shifts in OSA severity category in 77.9% of patients with nightly pulse-oximetry. Nevertheless, the inflammatory and metabolic parameters consistently supported the positive effects of LMP. Thus, treatment decision should be based more on clinical evaluation and outcomes than on derivatives from sleep studies.

Conclusion

Weight loss by LMP improved subclinical inflammation and insulin sensitivity among obese Chinese patients with moderate to severe OSA, irrespective of craniofacial restriction as determined by MMV.

Funding

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Disclosure

The results of this research have been previously published in:

1. Ng SSS, Tam WWS, Lee RWW, et al. Effect of weight loss and continuous positive airway pressure on obstructive sleep apnea and metabolic profile stratified by craniofacial phenotype: a randomized clinical trial. Am J Respir Crit Care Med 2022;205:711-20.

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Assistive listening devices for Chinese children with dyslexia: abridged secondary publication

ACS Kam *, PSH Lau, KCP Yuen, KKY Poon, KKH Chung

KEY MESSAGES

1. In our study, most Chinese children with dyslexia have significant difficulties in speech-in-noise perception and Cantonese tone identification and have significant language impairment.
2. Using assistive listening devices in classrooms for one academic year may improve literacy and auditory processing abilities in Chinese children with dyslexia.
3. Provision of such devices to students with dyslexia in schools may be considered, similar to provision of frequency modulated systems to students with hearing impairment in schools.

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Introduction

Dyslexia is defined as difficulty of learning to read and write despite adequate intelligence and education and in the absence of sensory impairment and neurological damage. It affects 5% to 10% of school-age children.[1] Dyslexia can result in poor academic performance and psychological distress.[2] Up to 10% of students in Hong Kong fall within the diagnostic criteria for dyslexia.[3]

Evidence to support a special intervention approach for dyslexia is limited.[2] Auditory-processing deficits in the dyslexic population have prompted the use of auditory approaches for intervention. Assistive listening devices are a promising intervention or management strategy for dyslexic children with auditory-processing deficits.[4] Dyslexic Chinese children commonly manifest auditory processing deficits. Enhancement in auditory processing ability may positively affect speech perception and phonological awareness; such positive effects may improve reading and language abilities. We hypothesised that dyslexic Chinese children may benefit from the use of assistive listening devices (frequency modulated systems) in classrooms.

Methods

First to fourth grade children who were diagnosed with dyslexia by professional psychologists were invited to participate. After obtaining written informed consent, participants were randomly assigned to either the intervention-control group or the control-intervention group. The intervention-control group received real device fitting in the first study period, followed by sham device fitting in the second study period, whereas the control-intervention group received sham device fitting in the first study period, followed by real device fitting in the second study period. Both study periods lasted for 10 months (one academic year). The assistive listening device was fitted monaurally and monitored according to the American Speech-Language-Hearing Association guidelines.[5] Assessments were performed at The Education University of Hong Kong by research assistants under supervision of speech therapists, audiologists, and a psychologist. Assessors were blinded to the intervention. Participants were assessed before and immediately after each of the two study periods. Primary outcome measures included literacy abilities (measured by a set of literacy tasks) and neural representation of speech (measured by consistency of auditory brainstem responses to sound). Secondary outcome measures included speech and language abilities.

Statistical analysis was on an intention-to-treat basis. Between-group differences at baseline were assessed by Fisher's exact test or Chi squared test. Repeated measures analysis of variance (ANOVA) was conducted for each outcome measure to evaluate intervention efficacy with assistive listening devices. Post hoc analyses for within-subject effects (repeated measure: time) were conducted for outcomes with significant time × group interactions to identify the two successive time points on which a significant difference was found. Statistical significance was set at $P<0.05$. Bonferroni corrections were applied for multiple comparisons with repeated measures ANOVA.

Results

27 girls and 48 boys (mean age, 9.1 years) were randomly assigned to one of the two groups. The

two groups were comparable in terms of baseline demographics and outcome measures.

First study period

At baseline assessment, the control group scored significantly higher in nonword repetition (P=0.029) and nonsense word repetition (P=0.046) than the intervention group. Repeated measure of ANOVA demonstrated a significant interaction effect between time and group in syntactic skills (F=5.002, P=0.029), Cantonese tone perception (F=6.630, P=0.13), and phonological awareness (F=5.144, P=0.027). The intervention group showed significantly more improvement in syntactic skills (P=0.029) and Cantonese tone perception ability (P=0.013) than the control group, whereas the control group showed significantly more improvement in phonological awareness than the intervention group (P=0.27).

Second study period

At baseline assessment, the intervention group scored significantly better in speech perception in noise (P=0.033), textual comprehension (P=0.010), nonword repetition (P=0.003), and nonsense word repetition (P=0.004) than the control group. Repeated measure ANOVA revealed significant interaction effect between time and group in auditory brainstem response (ABR) consistency to the speech sound /da/ (F=5.550, P=0.023), phonological awareness (F=5.442, P=0.024), Hong Kong Cantonese grammar (F=5.508, P=0.023), and word definition (F=4.394, P=0.041). The intervention group showed significantly more improvement in ABR consistency to /da/ than the control group (P=0.023), whereas the control group showed significant more improvement in Hong Kong Cantonese grammar (P=0.023), word definition (P=0.041), and phonological awareness (P=0.24) than the intervention group.

Discussion

The improved literary performance (sentence reconstruction) and auditory processing ability (tone perception) after the use of assistive listening devices supported our hypothesis that dyslexic Chinese children may benefit from assistive listening devices in classrooms. The intervention group showed significantly higher ABR consistency to the speech sound /da/ in the second study period, but no significant improvement in ABR consistency to any speech sounds was observed in the first study period. This study does not provide strong evidence to support long-term frequency modulated systems usage to reduce the variability of subcortical responses to sound and to improve the neural representation of speech. As literacy achievement and auditory processing abilities were enhanced in the first study period, the enhancement in acoustic clarity and stability in auditory processing may play a more critical role.

Most children showed significant difficulties in speech-perception-in-noise and Cantonese tone perception, compared with normative data. Future research to explore whether such tasks can be used as screening tools for dyslexia in children is warranted.

Conclusion

Assistive listening devices could enhance literacy abilities and auditory processing abilities in Chinese children with dyslexia. Provision of such devices to students with dyslexia in schools may be considered, similar to provision of frequency modulated systems to students with hearing impairment in schools.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#14150431). The full report is available from the Health and Medical Research Fund website (https://rfs1.fhb.gov.hk/index.html).

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Effect of feeding methods on intestinal microbiota of Chinese infants: abridged secondary publication

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KEY MESSAGES

1. Breastmilk-fed infants have fewer pathogenic bacteria and more beneficial bacteria in intestinal microbiota than formula-fed infants.
2. Direct and expressed breast milk feeding results in significantly fewer pathogenic bacteria in infants at 6 weeks of age.
3. Breastfeeding regardless of feeding mode (direct or expressed) is a modifiable factor that affects the infant gut microbiome and has potential short-term and long-term consequences for infant health later in life.

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Introduction

Infant gut microbiota plays an important role in intestinal homeostasis, development of the immune system, and protection against pathogens.[1] Bifidobacteria and Lactobacilli are the most important health-beneficial bacteria, whereas staphylococci and clostridia are potential pathogenic bacteria.[2] Disruption of the intestinal microbiota is associated with inflammatory bowel disease, necrotising enterocolitis, diabetes, obesity, cancer, allergies, and asthma.[3]

Breastmilk promotes a healthy gut microbiota by providing selective metabolic substrates for beneficial bacteria.[4] Exclusively breast-fed infants have more beneficial bacteria (such as Bifidobacterium and Lactobacillus) and fewer pathogenic bacteria, compared with formula milk–fed infants.[5] Nonetheless, infants in different geographical regions with different ethnic background may possess different types of gut microbiome profile. Studies from Asia or Chinese populations are limited.

There is a growing trend in expressed breast milk feeding among mothers of healthy term infants in developed countries. In Hong Kong, 84.6% of mothers had given expressed breast milk at some point; 14.6% and 20% of mothers had fed expressed breast milk within 1.5 and 3 months after birth, respectively.

The intestinal microbiota plays a critical role in infant development, and the type of feeding and mode of delivery may cause perturbations of microbial profiles. This study aims to compare infant microbiota profile between those fed directly at the breast, those fed expressed breast milk, and those fed formula milk. Methods of breast milk feeding may have short-term and long-term consequences for infant health later in life.

Methods

A total of 218 women with singleton pregnancies were recruited between August 2018 and December 2019. Recruitment was halted since January 2020 because home visits for stool collection was stopped during the COVID-19 pandemic. Participants were excluded if their infants were <37 weeks of gestation, had an Apgar score of <8 at 5 minutes, had a birthweight of <2500 g, had any severe medical conditions or congenital malformations, had been in special care unit for >48 hours, had been in neonatal intensive care unit, received a prescribed antibiotic, or had pre-existing gastrointestinal and immunodeficiency disease.

Infant feeding was recorded by a standardised questionnaire at recruitment and before the scheduled home visit at 6 weeks. Infant feeding was classified as direct breastfeeding, expressed milk feeding (>70% of feeding is expressed breastmilk), and formula milk feeding.

Infant stools were collected at a scheduled home visit when infants reached 6 weeks of age. Participants were instructed to place the diaper

with stool sample in a collection bag and keep it in a refrigerator until collection by trained research assistant using a container and a spoon. Containers were labelled with a unique number and date, time, and place of collection and placed in a cooler. The sample was immediately transported to laboratory with ice blocks and frozen at -80°C.

Total genomic DNA was extracted from 200 mg of faecal sample using QIAamp PowerFecal DNA Kit (Qiagen) according to the manufacturer instructions. The genomic DNA and its quality were quantified and checked. The 16S DNA library was prepared based on the Illumina protocol for 16S Metagenomic Sequencing Library Preparation. The 16S amplicons were generated using primers that span the hypervariable regions V3-V4 of the bacterial 16S rRNA gene with overhang adapters attached, with 25 cycles of polymerase chain reaction (PCR). Five μL of amplicon from each sample was used to generate indexed library using Nextera XT Index Kit v2, with eight cycles of PCR. These enriched libraries were validated by Qubit and quantitative PCR for quality control analysis. The indexed libraries were pooled in equimolar amounts. The pooled library was then denatured and diluted to the optimal loading concentration. Sequencing was performed using the MiSeq PE300 platform.

Using QIIME2 version 2019.7, reads were assembled, demultiplexed, and filtered against the SILVA reference database release 132. Chimeric filtering was performed using DADA2. For subsequent analyses, data were rarefied to 28 020 sequences per sample. Microbiota alpha diversity was assessed using Chao1, abundance-based coverage estimator (ACE), and observed amplicon sequence variants (ASVs) indices for species richness, whereas the Shannon index, Simpson index, and Faith's phylogenetic diversity (PD) were used as diversity estimation. Intestinal microbiota of infants were compared between the three feeding status groups using non-parametric Kruskal–Wallis test and Wilcoxon rank-sum test. Microbiota community structures were compared using permutational analysis of variance on unweighted unique fraction (UniFrac) distance and weighted UniFrac distance matrices with 9999 permutations. Beta diversity distances were visualised using principal coordinate analysis. Differentially abundant genera in breastfed, expressed milk–fed, and formula milk–fed samples were tested using the analysis of composition of microbiomes. The percentage of Bifidobacterium and differentially abundant taxa were compared using the Kruskal–Wallis test and Wilcoxon rank-sum test.

Results

As of December 2019, 218 women were recruited and their infants were classified as directly breastfed (n=84), expressed milk fed (n=50), and formula milk fed (n=84). There was significant difference between the three groups in terms of maternal age, maternal education, and family income, intention to return to work post-partum, partner's infant feeding preference, and mode of birth (Table). There was no significant difference between the three groups in terms of parity and length of residence.

In alpha diversity analyses, compared with breastfed infants, formula milk–fed infants had a higher Chao1 (55.0 vs 40.0, P=8.3e-10), ACE (55.0 vs 40.0, P=8.6e-10), and observed ASVs (53 vs 39, P=4.7e-09) abundance in gut microbiota. This indicates higher species richness in formula milk–fed infants. A similar difference of species abundance was found between the formula milk group and the expressed milk group in terms of Chao1 (55.0 vs 43.5, P=1.12e-05), ACE (55.0 vs 43.5, P=1.15e-05), and observed ASVs (53 vs 41, P=4e-05). However, there was no significant difference in species abundance between breastfed infants and expressed milk–fed infants in terms of Chao1 (40.0 vs 43.5, P=0.33), ACE (40.0 vs 43.5, P=0.34), and observed ASVs (39 vs 41, P=0.32).

Shannon index, Simpson index, and Faith's PD were used to determine the microbial diversity. The species diversity was significantly higher in formula milk–fed infants than in breastfed infants (Shannon index: P=0.0137, q=0.021; Simpson index: P=0.1020, q=0.1525; Faith's PD: P=0.0002, q=0.0005) and expressed milk–fed infants (P=0.0044, q=0.0132; P=0.0175, q=0.0522; and P=0.0156, q=0.023, respectively), but there was no significant difference between breastfed and expressed milk–fed infants (P=0.6048, q=0.6; P=0.3758, q=0.38; and P=0.174, q=0.17, respectively).

Principal coordinate analysis was used to determine the varieties of community structure of individual samples from the three groups. The overall beta diversity of the community structure of microbiota was evaluated using weighted UniFrac and unweighted UniFrac analyses. Both beta diversity indices indicated that the structure of microbiota significantly differed: weighted UniFrac (overall P=0.0011) and unweighted UniFrac (overall P=0.0001). In pairwise comparisons of the three groups using weighted UniFrac, formula milk–fed infants were strongly associated with a distinct community structure from breastfed infants (pseudo F=4.0, P=0.0038, q=0.0057) or expressed milk–fed infants (pseudo F=4.7, P=0.0005, q=0.0015). There was no significant difference between breastfed infants and expressed milk–fed infants using weighted UniFrac (pseudo F=1.2, P=0.2911, q=0.2911); this indicates that both feeding methods resulted in similar relative abundance of microbiota.

At the phylum level, >90% of the bacterial sequences were assigned to Proteobacteria,

TABLE. Characteristics of participants

Characteristic	Total (n=218)*	Direct breastfeeding (n=84)*	Expressed breast milk feeding (n=50)*	Formula milk feeding (n=84)*	P value
Maternal age, y					0.03
18-29	51 (23.4)	12 (14.3)	11 (22.0)	28 (33.3)	
30-34	107 (49.1)	45 (53.6)	29 (58.0)	33 (39.3)	
≥35	60 (27.5)	27 (32.1)	10 (20.0)	23 (27.4)	
Maternal education					<0.001
Below university degree	128 (58.7)	41 (48.8)	21 (42.0)	66 (78.6)	
University degree or above	90 (41.3)	43 (51.2)	29 (58.0)	18 (21.4)	
Monthly family income, HK$					0.002
<20 000	31 (14.2)	12 (14.3)	3 (6.0)	16 (19.1)	
20 000-34 999	64 (29.4)	20 (23.8)	10 (20.0)	34 (40.5)	
≥35 000	123 (56.4)	52 (61.9)	37 (74.0)	34 (40.5)	
Length of residence in Hong Kong, y					0.07
<10	25 (11.5)	13 (15.5)	1 (2.00)	11 (13.1)	
≥10	58 (26.6)	24 (28.6)	11 (22.0)	23 (27.4)	
Since birth	135 (61.9)	47 (56.0)	38 (76.0)	50 (59.5)	
Intention to return to work post-partum					0.007
No	81 (37.2)	29 (34.5)	11 (22.0)	41 (48.8)	
Yes	137 (62.8)	55 (65.5)	39 (78.0)	43 (51.2)	
Parity					0.081
Primiparous	88 (40.4)	26 (31.0)	23 (46.0)	39 (46.4)	
Multiparous	130 (59.6)	58 (69.1)	27 (54.0)	45 (53.6)	
Partner's infant feeding preference					<0.001
Breastfeeding	87 (39.9)	51 (60.7)	31 (62.0)	5 (6.0)	
No preference	92 (42.2)	32 (38.1)	13 (26.0)	47 (56.0)	
Formula milk and mixed feeding	39 (17.9)	1 (1.2)	6 (12.0)	32 (38.1)	
Mode of birth					0.03
Spontaneous vaginal	157 (72.0)	65 (77.4)	41 (82.0)	51 (60.7)	
Assisted vaginal	9 (4.1)	5 (6.0)	2 (4.0)	2 (2.4)	
Planned caesarean	32 (14.7)	9 (10.7)	5 (10.0)	18 (21.4)	
Emergency caesarean	20 (9.2)	5 (6.0)	2 (4.0)	13 (15.5)	

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

Bacteroidetes, Firmicutes, Actinobacteria, Verrucomicrobia, Fusobacteria, Patescibacteria, and Epsilonbacteraeota. The relative abundance of Proteobacteria (41.5%±22.6%; range, 0.1%-90.8%), Bacteroidetes (19.4%±22.6%; range, 0%-83.3%), Firmicutes (19.7%±15.9%; range, 0.6%-80.2%), and Actinobacteria (18.2%±16.8%; range, 0%-87%) were the most dominant gut microbiota in the three groups of infants (Fig 1). The breastfed and expressed milk–fed infants exhibited similar relative abundance among all these phyla. However, gut microbiota that were significantly higher in formula milk–fed infants than in breastfed infants and expressed milk–fed infants were Firmicutes (21.05% vs 12.81% vs 10.8%, P<0.0005) and Verrucomicrobia (2.22% vs 0% vs 0%, P<0.05).

Given the limited association of feeding mode with the main objective taxa, analysis of composition of microbiomes was applied to test differentially abundant taxa caused by feeding practice. Two families and ten genera including *Enterobacteriaceae*, *Enterococcaceae*, *Staphylococcus*, *Haemophilus*, *Enterococcus*, *Corynebacterium 1*, *Veillonella*, *Acinetobacter*, *Serratia*, *Clostridium sensu stricto 1*, *Cutibacterium*, and *Gemella* were found to be different (Fig 2). Relative to formula milk feeding, breastfeeding and expressed milk feeding were associated with increasing relative abundance of

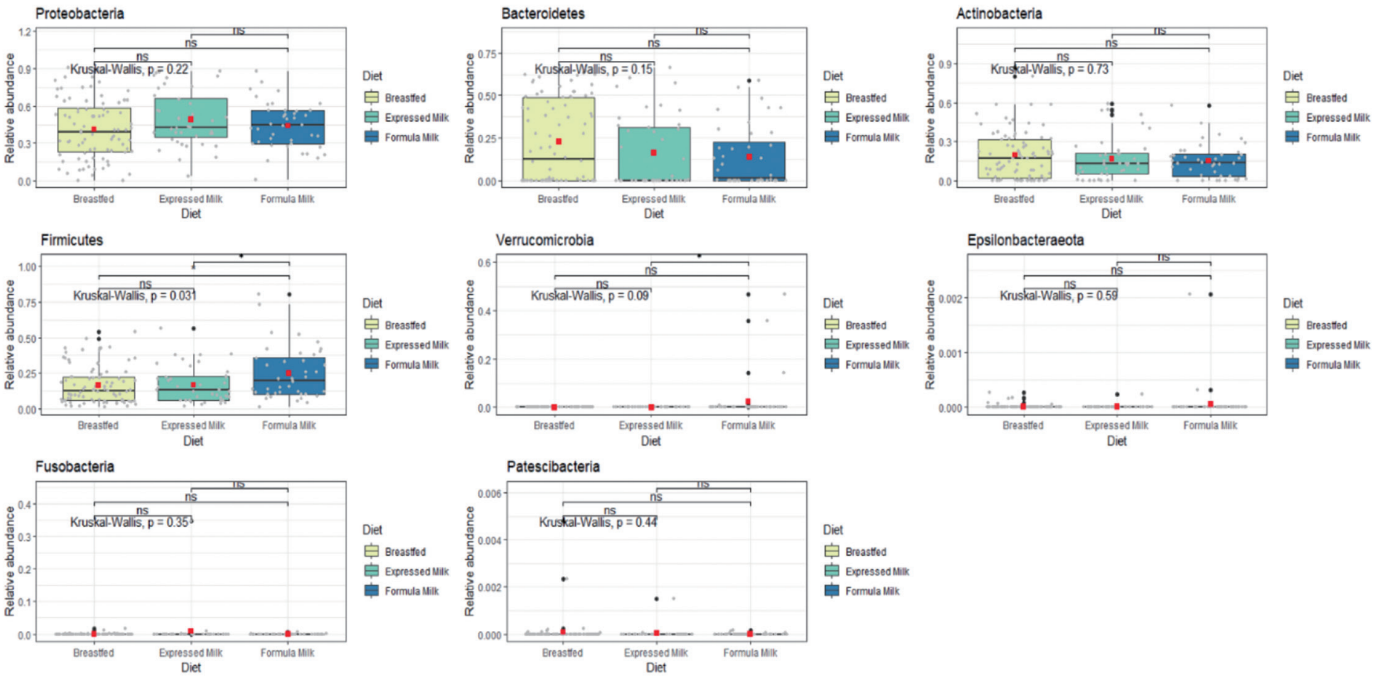

FIG 1. Relative abundance of dominant phyla across diet groups

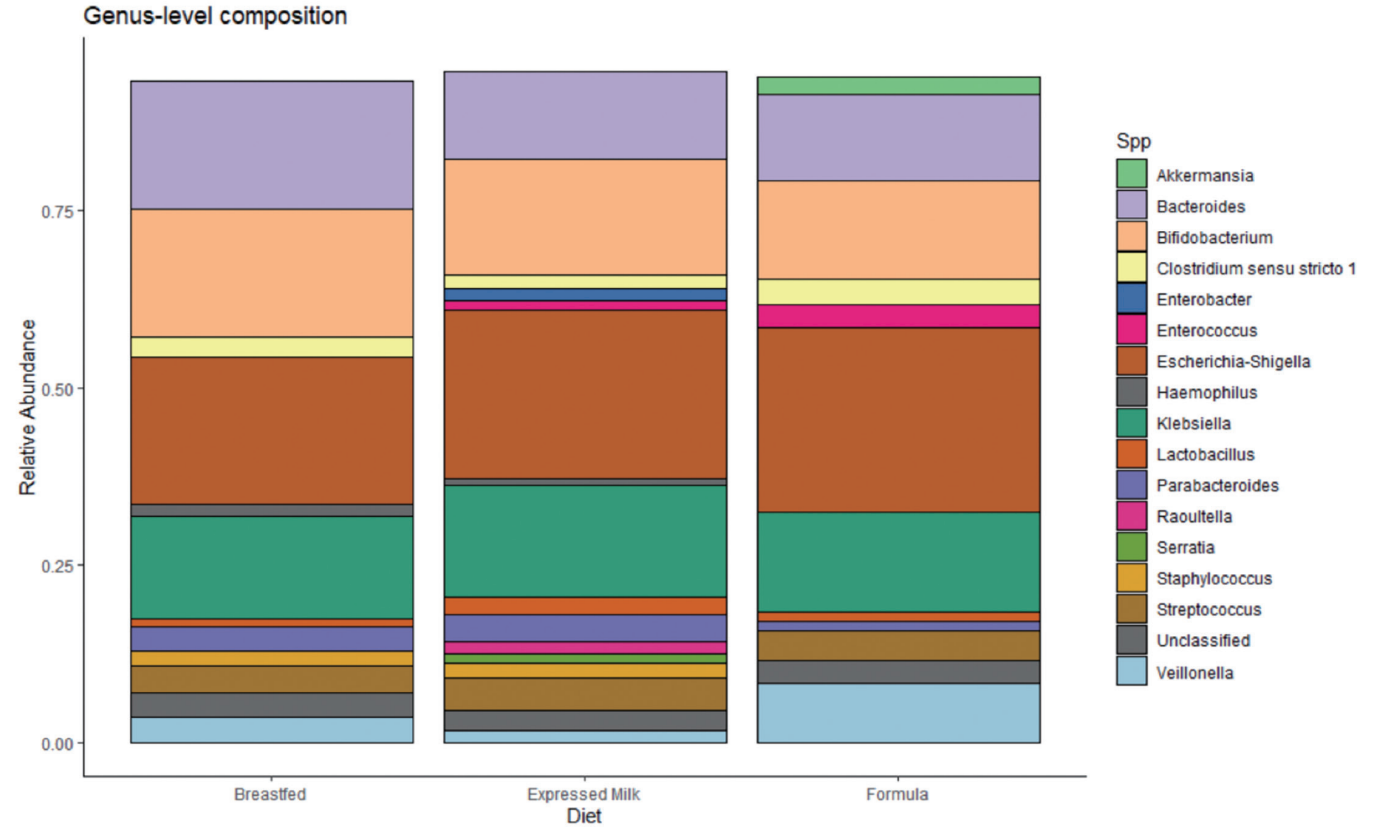

FIG 2. Relative abundance comparison of analysis of composition of microbiomes identified differentially abundant taxa

Staphylococcus (0.05% vs 0.9% vs 1.0%, P=9.10E-20). However, some decreased taxa were found in the formula milk group including *Haemophilus*, *Corynebacterium*, *Serratia*, *Cutibacterium*, and *Gemella* (Fig 2). Most notably, formula milk–fed infants had a significant increase of *Veillonella* (3.10% vs 0.51% vs 0.19%, P=3.1e-07) and *Enterococcus* (1.09% vs 0.02% vs 0.02%, P=2.37e-11) [Fig 2].

Relative to formula milk–fed infants, breastfed infants and expressed milk–fed infants showed no difference in the relative abundance of most tested genera (Fig 2). *Acinetobacter* (a type of potentially pathogenic bacteria associated with antibiotic resistance) was found more abundant in expressed milk–fed infants than breastfed infants and formula milk–fed infants (0.25% vs 0.03% vs 0.013%, P=0.0016, Fig 2).

Discussion

Most of microbiota compositions were similar in breastfed and expressed milk–fed infants. Nonetheless, there were some minor genera (*Acinetobacter* and *Serratia*) that might be associated with expressed milk feeding. *Acinetobacter* (a type of potentially pathogenic bacteria associated with antibiotic resistance) was found more abundant in expressed milk–fed infants than breastfed infants and formula milk–fed infants. Pumping breast milk may be associated with these minor genera difference. It is possible that habitual pumping or the process of storage (freezing and thawing) may alter the composition of minor genera differences in the gut microbiome. Breastmilk feeding practice does not alter the infant microbial profile regardless of feeding mode; gut microbiota of breastfed and expressed milk–fed infants is more commonly colonised by aerobic organisms, whereas that of formula milk–fed infants are enriched with anaerobic organisms such as Bacteroides and Veillonella. Future research is warranted to examine the antibiotic resistance genes between these microbial communities and to determine how they are impacted by breast milk feeding practices.

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