SUPPLEMENT 7

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Health and Medical Research Fund

Research Dissemination Reports

醫療衞生研究基金

研究成果報告

Non-communicable diseases and risk factors
非傳染性疾病及風險因素

Cancer
癌症

Neurology
神經病學

Health services
衞生服務

Infectious diseases
傳染病

Supplement 7

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Health and Medical Research Fund

Research Dissemination Reports

INFECTIOUS DISEASES

Editorial

Dissemination reports are concise informative reports of health-related research supported by the Health and Medical Research Fund administered by the Health Bureau. In this edition, we present 10 dissemination reports of projects related to non-communicable diseases and risk factors, cancer, neurology, health services, and infectious diseases. In particular, research findings of three projects may provide insights to enhance clinical practices and help inform health policy formulation in Hong Kong.

Colorectal cancer (CRC) is the second commonest cancer in terms of the number of new cases and cancer deaths in 2020 in Hong Kong.[1] CRC is curable if diagnosed at an early stage of development. Therefore, screening is of paramount importance in early CRC detection. Foo et al[2] evaluated the accuracy of a non-invasive screening method using a panel of blood microRNA for identifying CRC patients, and compared the cost-effectiveness of microRNA against conventional CRC screening strategies. The resulting serum microRNA panel had a sensitivity of 85.8%, specificity of 80.95% with positive predictive value of 86.9% and negative predictive value of 79.4%. Combining serum microRNA test and colonoscopy is a more cost-effective method than colonoscopy alone.

Myopia is the most common eye condition in the world and the number of cases is projected to increase further. High myopia can cause severe visual impairment including myopic macular degeneration, retinal detachment, glaucoma, and cataract, leading to impaired quality of life and burden on the individual and healthcare system. Various interventions have been developed to control the progression of myopia. Lian et al[3] evaluated the cost-effectiveness of Defocus Incorporated Multiple Segments (DIMS) spectacle lenses. They found that the concept of myopia control is value for money from the societal perspective, in preventing eye complications and severe visual impairment, and is cost-effective in terms of cost per quality adjusted life-year gained. A government-subsidised myopia control programme could be a cost-effective option to improve equity of access to treatment options.

Influenza vaccine efficacy varies widely depending on the degree of similarity between the vaccine haemagglutinin and that present on circulating virus strains. Some classes of antibodies can cross-react with seasonal, pandemic, and avian influenza viruses and may be able to protect against infection or severity of disease after infection. Valkenburg et al[4] utilised a biobank of immune serum from children vaccinated in 2008 with trivalent seasonal influenza vaccines and tracked them over the next 5 years to determine if the magnitude of their antibody-mediated responses is enhanced by vaccination resulting in reduced risk of influenza infection. They found that pandemic haemagglutinin IgG responses are boosted by recent seasonal vaccination but decline within 1 year to baseline by 5 years. Vaccination increased IgG1 responses to vaccine and a range of pandemic influenza virus proteins, compared with unvaccinated children. Seasonal influenza vaccination should be encouraged to protect against pandemic influenza viruses where the cross reactivity may provide some residual protection.

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Combining interactive communication and nicotine replacement therapy for smokers: abridged secondary publication

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KEY MESSAGES

1. Mobile healthcare enables high-reach, low-cost, and personalised smoking cessation support.
2. We assessed the effectiveness of interactive communication technologies (instant messaging and chatbot) plus nicotine replacement therapy for smoking cessation in 664 smokers in Hong Kong.
3. Compared with controls, the intervention group had higher rates of abstinence at 6 months (3.9% vs 3.0%, odds ratio [OR]=1.31) and 12 months (5.4% vs 4.5%, OR=1.21), but the differences were not statistically significant.
4. Our findings have guided the establishment of two chatbots to promote smoking cessation services and COVID-19 vaccination.

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Introduction

Mobile healthcare (mHealth) enables high-reach, low-cost, and personalised smoking cessation (SC) support.[1] Compared with brief advice alone, combining instant messaging (IM)-based intervention with brief advice led to a higher validated abstinence rate among smokers in Hong Kong (odds ratio [OR]=1.68, 95% confidence interval [CI]=1.03-2.74).[2] Artificial intelligence chatbots can supplement human advisors in IM for behavioural support. Nicotine replacement therapy (NRT) combined with behavioural intervention is recommended for achieving long-term abstinence.[3] The provision of NRT sampling has been efficacious to increase quit attempts among unmotivated smokers.[4] This study aimed to determine the effectiveness of combining interactive communication technologies (IM and chatbot) with NRT sampling for SC among smokers in Hong Kong.

Methods

This study was conducted between August 2019 and May 2020. We proactively approached smokers at various locations in Hong Kong. Inclusion criteria were (1) individuals aged ≥18 years with a habit of smoking at least one cigarette daily, (2) exhaled carbon monoxide level of ≥4 parts per million, (3) having a smartphone and agreeing to install IM apps and a chatbot, and (4) Hong Kong residency with the ability to read and communicate in Chinese. Smokers were excluded if they had psychiatric or psychological diseases and were taking psychotropic medications; were using cessation medication, NRT, or other SC services; or had contraindications to NRT use.

Participants were randomly assigned to the intervention or control group. Participants in both groups received brief advice based on the AWARD model (Ask, Warning, Advice, Referral, Do-it-again). Participants were asked about their smoking history (Ask); warned about the harms of continued smoking using the test results of exhaled carbon monoxide level and a health warning leaflet (Warn); advised to quit as soon as possible by using NRT or SC services (Advise); and offered referral to SC services, which are free to Hong Kong residents and provide evidence-based SC treatments such as behavioural counselling, NRT, and acupuncture (Refer). The above advice was repeated for relapsed smokers (Do-it-again).

Participants in the intervention group received 1 week of free NRT sampling (Nicotinell; GlaxoSmithKline, Brentford, London, UK) and 12

weeks of personalised behavioural support using interactive communication technologies guided by social cognitive theory and the transtheoretical model. Regular instant messages were tailored to the participants' surnames, sociodemographic characteristics, smoking habit at baseline, and updated smoking status. In total, 21 messages were sent according to a pre-set schedule: once daily for 1 week, twice weekly for 4 weeks, and once weekly for the remaining 7 weeks. The schedule was adjusted according to each participant's stage of change (quit date set at baseline) as determined via the transtheoretical model and as requested by smokers during IM conversations. In addition, synchronous, personalised, and interactive psychosocial support was delivered by trained SC advisors through IM conversations. Advisors provided real-time responses such as support to avoid or manage situations with high risk of smoking. Advisors periodically sent proactive IM messages to initiate the conversation (eg, asking about recent SC progress) and delivered evidence-based advice guided by social cognitive theory and the transtheoretical model. Advisors actively referred smokers to cessation services if they expressed such a need. Furthermore, SC advisors proactively sent six reminders of the URL of a chatbot called 'Quit Buddy' through IM once every 2 weeks for 12 weeks. The chatbot content did not change during the trial.

Participants in the control group received the same AWARD intervention at baseline, regular SMS messages regarding generic advice about healthy lifestyles and reminders to participate in follow-up surveys and biochemical validation for quitting.

Primary outcomes were rates of validated smoking abstinence at 6 and 12 months after treatment initiation. Secondary outcomes included self-reported 7-day point prevalence and continuous (24-week) abstinences, quit attempts, smoking reduction (ie, self-reported reduction in number of cigarettes per day by ≥50% of the baseline amount), and cessation service use at 6 and 12 months.

The validated quit rate for participants who received AWARD advice with active referral to SC services was approximately 9% at the 6-month follow-up.[5] Considering an estimated effect size of 1.8 derived from a meta-analysis,[1] along with 80% power and a 1:1 allocation ratio, the sample size required to identify a significant difference (with two-sided type I error of 0.05) in biochemically validated quit rates between groups was 664 (332 per group).

Analyses were based on an intention-to-treat protocol. Logistic regression analysis was used to compare SC outcomes between groups. Sensitivity analyses were conducted to assess the robustness of the intervention effect on outcomes.

Results

Of 711 smokers screened, 664 were eligible and consented to participate. The retention rates were 69.9%, 67.2%, and 73.2% at 3, 6, and 12 months, respectively. Retention rates were similar between groups (P=0.49-0.95). The two groups were comparable in terms of baseline characteristics (P=0.09-0.99, Table 1). Most participants were men (74.4%) and were aged 18 to 39 years (62.5%). Of the participants, 62.3% had low cigarette dependence, 59.6% had never attempted to quit, and 51.7% did not intend to quit within 30 days.

Compared with the control group, the intervention group had higher rates of biochemically validated abstinence at 6 months (3.9% vs 3.0%, OR=1.31, 95% CI=0.57-3.04) and 12 months (5.4% vs 4.5%, OR=1.21, 95% CI=0.60-2.45), but the differences were not statistically significant (Table 2). There were no significant differences in self-reported 7-day point-prevalent abstinence, self-reported 24-week continuous abstinence, smoking reduction, or use of SC services at 6 and 12 months. Compared with the control group, the intervention group had higher rates of quit attempts at 6 months (47.0% vs 38.0%, OR=1.45, 95% CI=1.06-1.97). Sensitivity analyses yielded similar results.

Discussion

Interactive communication technologies plus NRT did not significantly improve SC outcomes including validated abstinence, self-reported 7-day point-prevalent abstinence, self-reported 24-week continuous abstinence, smoking reduction, or use of SC services at 6 and 12 months. However, the intervention significantly increased the rate of quit attempts at 6 months, but this effect was not sustained at 12 months. The real-world effect might have been underestimated because the control group received AWARD and similarly scheduled SMS messages regarding general health. Thus, the effect size of the present study was smaller than the 1.8 reported in a meta-analysis,[1] although a direct comparison might not be feasible because of heterogeneity in study settings, smoking characteristics, and intervention components. In addition, the present study included 59.6% of participants who had never attempted to quit, which differs from previous SC trials that included smokers with intention to quit only.

The present study had several limitations. First, our findings may not be generalisable to populations with a more balanced sex ratio among smokers or regions with limited SC services. Second, considering the low intervention engagement, the beneficial effects may have been underestimated. Third, interaction of the effects of each intervention component was beyond the scope of the

TABLE 1. Baseline characteristics of participants (n=664)

Characteristic	Intervention (n=332)*	Control (n=332)*	P value
Sex			0.72
Male	249 (75.0)	245 (73.8)	
Female	83 (25.0)	87 (26.2)	
Age, y			0.92
18-29	99 (30.3)	103 (31.9)	
30-39	104 (31.8)	109 (33.8)	
40-49	78 (23.9)	69 (21.4)	
50-59	35 (10.7)	31 (9.6)	
≥60	11 (3.4)	11 (3.4)	
Marital status			0.17
Single	154 (51.2)	175 (58.3)	
Married/cohabited	128 (42.5)	112 (37.3)	
Divorced/separated/widowed	19 (6.3)	13 (4.3)	
Educational attainment			0.94
Primary or below	2 (0.6)	2 (0.6)	
Secondary	160 (48.8)	161 (50.2)	
Tertiary	166 (50.6)	158 (49.2)	
Employment status			0.42
Employed	278 (85.0)	282 (87.9)	
Unemployed	41 (12.5)	30 (9.4)	
Retired	8 (2.5)	9 (2.8)	
Monthly household income, HK$			0.99
≤19999	48 (16.5)	48 (16.8)	
20000-29999	90 (30.9)	87 (30.4)	
≥30000	153 (52.6)	151 (52.8)	
Daily cigarette consumption, sticks			0.38
1-10	232 (69.9)	236 (71.1)	
11-20	91 (27.4)	92 (27.7)	
≥21	9 (2.7)	4 (1.2)	
Time to first cigarette of the day, minutes			0.22
>60	97 (29.3)	104 (31.3)	
31-60	57 (17.2)	40 (12.1)	
6-30	89 (26.9)	87 (26.2)	
≤5	88 (26.6)	101 (30.4)	
Cigarette dependence (Heaviness of Smoking Index)			0.46
Low (0-2)	213 (64.2)	201 (60.5)	
Moderate (3-4)	113 (34.0)	127 (38.3)	
High (5-6)	6 (1.8)	4 (1.2)	
Previous quit attempt			0.34
Never	204 (61.5)	192 (57.8)	
Ever	128 (38.6)	140 (42.2)	
Intention to quit			0.10
Within next 7 days	84 (25.3)	75 (22.6)	
Within next 30 days	92 (27.7)	70 (21.1)	
Within next 60 days	19 (5.7)	24 (7.2)	
Not decided yet	137 (41.3)	163 (49.1)	0.41
Perceptions of quitting (1-10)			
Importance	7.1±2.1	6.8±2.1	0.10
Difficulty	7.3±2.5	7.0±2.4	0.09
Confidence	5.9±2.0	5.7±2.1	0.16

* Data are presented as No. (%) of participants; total number of participants in each group may not equal to 332 owing to missing data

TABLE 2. Primary and secondary outcomes (n=664)

	Intervention (n=332)*	Control (n=332)*	Logistic regression model†	P value	Complete case analysis†	P value	Multiple imputation†	P value
Validated abstinence								
6 months	13 (3.9)	10 (3.0)	1.31 (0.57-3.04)	0.53	1.34 (0.58-3.13)	0.49	1.22 (0.53-2.82)	0.64
12 months	18 (5.4)	15 (4.5)	1.21 (0.60-2.45)	0.59	1.22 (0.60-2.47)	0.59	1.14 (0.56-2.33)	0.72
Self-reported 7-day point-prevalent abstinence								
6 months	32 (9.6)	28 (8.4)	1.12 (0.68-1.97)	0.59	1.19 (0.69-2.05)	0.53	1.09 (0.65-1.84)	0.74
12 months	34 (10.2)	32 (9.6)	1.07 (0.64-1.78)	0.80	1.07 (0.64-1.80)	0.79	1.14 (0.68-1.92)	0.61
Self-reported 24-week continuous abstinence								
6 months	14 (4.2)	19 (5.7)	0.73 (0.36-1.47)	0.37	0.91 (0.49-1.72)	0.78	0.91 (0.48-1.72)	0.78
12 months	21 (6.3)	20 (6.0)	1.05 (0.56-1.98)	0.87	0.88 (0.49-1.59)	0.67	0.88 (0.49-1.59)	0.67
Smoking reduction by ≥50% of baseline								
6 months	59 (17.8)	54 (16.3)	1.13 (0.75-1.71)	0.55	1.17 (0.76-1.82)	0.48	1.12 (0.73-1.71)	0.61
12 months	80 (24.1)	67 (20.2)	1.28 (0.88-1.85)	0.20	1.33 (0.89-1.99)	0.16	1.34 (0.90-2.00)	0.15
Quit attempt								
6 months (cumulative)	156 (47.0)	126 (38.0)	1.45 (1.06-1.97)	0.019	1.51 (1.05-2.17)	0.026	1.37 (0.98-1.91)	0.068
12 months (cumulative)	179 (53.9)	159 (47.9)	1.27 (0.94-1.73)	0.12	1.38 (0.96-1.99)	0.08	1.24 (0.88-1.77)	0.22
Use of smoking cessation services								
6 months (cumulative)	32 (9.6)	21 (6.3)	1.58 (0.89-2.80)	0.12	1.64 (0.92-2.95)	0.10	1.66 (0.94-2.94)	0.08
12 months (cumulative)	42 (12.7)	33 (9.9)	1.31 (0.81-2.13)	0.27	1.34 (0.81-2.19)	0.25	1.39 (0.86-2.25)	0.18

* Data are presented as No. (%) of participants
† Data are presented as odds ratio (95% confidence interval)

present study. Nevertheless, these components independently demonstrated effectiveness in our previous SC trials.[2,4,5]

Our findings guided subsequent research to enhance engagement, specifically concerning interactive communication technologies, to maximise intervention efficacy. We have developed a WhatsApp chatbot called 'Dr Wise' to promote SC services (https://wa.me/85223328977) in collaboration with the Tung Wah Group Hospitals Integrated Centre on Smoking Cessation. We also developed a web-based chatbot 'Vac chat, fact check' to promote COVID-19 vaccination.

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Disclosure

The results of this research have been previously published in:
1. Guo N, Luk TT, Wu YS, et al. Effect of mobile interventions with nicotine replacement therapy sampling on long-term smoking cessation in community smokers: a pragmatic randomized clinical trial. Tob Induc Dis 2023;21:44.

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Environment-wide and epigenome-wide association study of adiposity in 'Children of 1997' birth cohort: abridged secondary publication

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KEY MESSAGES

1. We identified several potential targets for obesity prevention including maternal exposure to second-hand smoke, consumption of artificially sweetened beverages, earlier puberty, and binge eating. We also identified several methylation loci associated with adiposity.
2. Identification of potential drivers of adiposity in Hong Kong Chinese individuals helps development of health policy interventions and future research.

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Introduction

Early-life adiposity persists into adulthood and increases the risks of multiple chronic diseases. Most nutritional studies focus on specific dietary factors; however, dietary patterns often co-occur and are difficult to distinguish from many other exposures. Environment-wide association studies (EWAS) enable various exposures across the human environmental exposome to be tested in a high-throughput manner, similar to genome-wide association studies that explore genetic effects.[1]

Effective treatments for obesity are limited, partly owing to limited understanding of the underlying molecular pathways. DNA methylation, which refers to the addition of a methyl group at the 5′ position of a cytosine residue in DNA, can modulate gene expression and thus influence an individual's susceptibility to obesity or obesity-related chronic diseases.[2] Unlike genetic variants, DNA methylation statuses are modifiable and may change in response to environmental factors or disease. Therefore, study results of Western populations may not be generalisable to Chinese populations because of differences in environmental exposure and economic development history.

Hong Kong can provide unique insights concerning health determinants, because it has mixed Western and Chinese cultures. Most Chinese people in Hong Kong are first-, second-, or third-generation migrants from neighbouring Guangdong Province in southern China. Their dietary habits are similar to those in southern China but also influenced by Western culture. Although active smoking among Chinese mothers was rare, maternal exposure to second-hand smoke during pregnancy was common before the implementation of a smoking ban in public places and workplaces in 2007 in Hong Kong. Moreover, most long-term studies involve populations of European descent in developed countries. Thus, a study of young Chinese people in Hong Kong may help to determine whether these associations reflect specific socioeconomic contexts or biological factors. For example, the associations of breastfeeding with childhood and adolescent adiposity in the 'Children of 1997' birth cohort are higher than associations typically present in Western settings.[3] We thus conducted an environment-wide and epigenome-wide association study to identify potential drivers of adiposity.

Methods

This study was based on the 'Children of 1997' birth cohort in Hong Kong.[4] Participants were recruited after birth in April and May 1997 at all 49 Maternal and Child Health Centres (MCHCs) in Hong Kong, which provide free check-ups and immunisations; the study included 88% of births in that period. A self-administered questionnaire in Chinese was used to collect baseline information concerning family, education, and birth characteristics, as well as infant feeding and second-hand smoke data. The initial study was primarily designed to provide a short-term assessment of the effects of second-hand smoke, and it included follow-up via the MCHCs until 18 months. In 2005, with support from the Health and Health Services Research Fund and Health and Medical Research Fund, we further collected data regarding infant characteristics, serious morbidities, childhood adiposity, pubertal development, migration history, and socioeconomic

status. Regular updates about subsequent growth were obtained from the Student Health Service. In 2007, with support from The University of Hong Kong University Research Committee Strategic Research Theme of Public Health, we re-established contact with the cohort and conducted several follow-up studies, including three questionnaire/telephone surveys and an in-person Biobank clinical follow-up at age ~17.5 years. More than 3500 participants attended the Biobank clinical follow-up, and their blood samples were stored. In 2020 (at age ~23 years), we conducted a follow-up survey to obtain updated information about anthropometric measurements.

Body mass index (BMI) was assessed by bioelectrical impedance analysis using a Tanita segmental body composition monitor (Tanita BC-545, Tanita, Tokyo, Japan). Waist and hip circumferences were measured twice with a tape measure. At age ~23 years, 700 participants were randomly selected from individuals with available blood samples and BMI below the 25th centile or above the 75th centile to complete a questionnaire including anthropometric measurements. A total of 308 participants replied and provided their waist, hip, height, and body weight information.

DNA methylation was examined in 288 of the 308 participants. Two samples with a sex mismatch were excluded; thus, 286 samples (168 women and 118 men) were included in the EWAS. After excluding non-CpG probes and probes located on sex chromosomes, 843 393 probes remained for analyses. Environmental exposures were defined broadly. After excluding exposures with ≥50% missing values, 370 exposures were included and classified into 13 categories: demographic, socioeconomic, family history, infant feeding, maternal information, maternal diet, diet, health status, physical activity, moods and feelings, school and academic performance, sleep, and pubertal timing. Univariable linear regression was used to assess associations of each of the 370 exposures with indicators of adiposity. Exposures that reached the Bonferroni-corrected significance threshold ($P<0.05/370 = 1.36*10^{-4}$) were included for multivariable linear regression that controlled for potential confounders. Exposures that had change-in-estimate ratios >50% were excluded. We replicated associations in the follow-up survey (n=308) and excluded associations with discordant directions.

In the epigenome-wide association study, because of the heteroscedasticity in methylation beta-values, robust linear regression models were used to determine associations of each CpG with BMI and waist-to-hip ratio (WHR) at age ~23 years, with adjustment for potential confounders. A Benjamini-Hochberg–corrected false discovery rate of <0.05 was considered statistically significant.

Results

A total of 3618 participants who attended the Biobank clinical follow-up at age ~17.5 years were included for analysis (Fig 1). After Bonferroni correction, 30 associations with BMI and 20 associations with WHR remained. After controlling for confounders, 25 associations with BMI and 11 associations with WHR remained. At age ~23 years, 25 associations with BMI and 8 associations with WHR had a consistent direction.

At age ~17.5 years, higher BMI was associated with sex, maternal exposure to second-hand smoke, diet, physical activity, health status, earlier puberty, and binge eating, whereas lower BMI was associated with consumptions of sweets and chocolate and a history of nightmares. At age ~23 years, most exposures showed consistent directions of association. However, the amount and frequency of chocolate consumption were not associated with BMI. Associations with WHR were similar to associations with BMI. Sex, consumption of artificially sweetened beverages (ASBs), and health status were associated with WHR at age ~17.5 years and age ~23 years.

In the epigenome-wide association study of 286 participants, 21 CpGs were identified for BMI in the genes *RBM16*, *SCN2B*, *AGPAT4*, *TFCP2*, *SLC24A4*, *TECPR2*, *KSR1*, *RPTOR*, *GTF3C3*, *ZNF827*, *TXNDC15*, *C2*, and *RPS6KA2*, whereas 18 CpGs were identified for WHR in the genes *LANCL2*, *C6orf195*, *MIR4535*, *CTRL*, *LYRM9*, *DCDC2*, *DIRC3*, *RPS6KA2*, *LPP*, *NFIC*, *MIR7641-2*, *ZNF141*, *RNF213*, *OPA3*, and *RRS1* (Fig 2). cg14630200 in *RPS6KA2* was a shared CpG for both BMI and WHR.

Discussion

We confirmed the risk factors for adiposity (maternal exposure to second-hand smoke and consumption of ASBs) and replicated null associations for sugar-sweetened beverages, breastfeeding, and milk consumption frequency. We also identified several CpGs associated with BMI and WHR.

Children who consume more ASBs have a higher BMI. However, association between sugar-sweetened beverages and adiposity was not found. The difference might have arisen because few participants regularly consumed sugar-sweetened beverages (only 6.8% reported daily consumption),[5] whereas 43% of participants reported daily consumption of ASBs. In addition, binge eating increased childhood BMI. Earlier puberty was associated with a higher subsequent BMI in girls. Clarification regarding this bi-directional association is worthwhile.

In the epigenome-wide association study, *RPS6KA2* was a shared gene for BMI and WHR, consistent with the results of previous studies.[2]

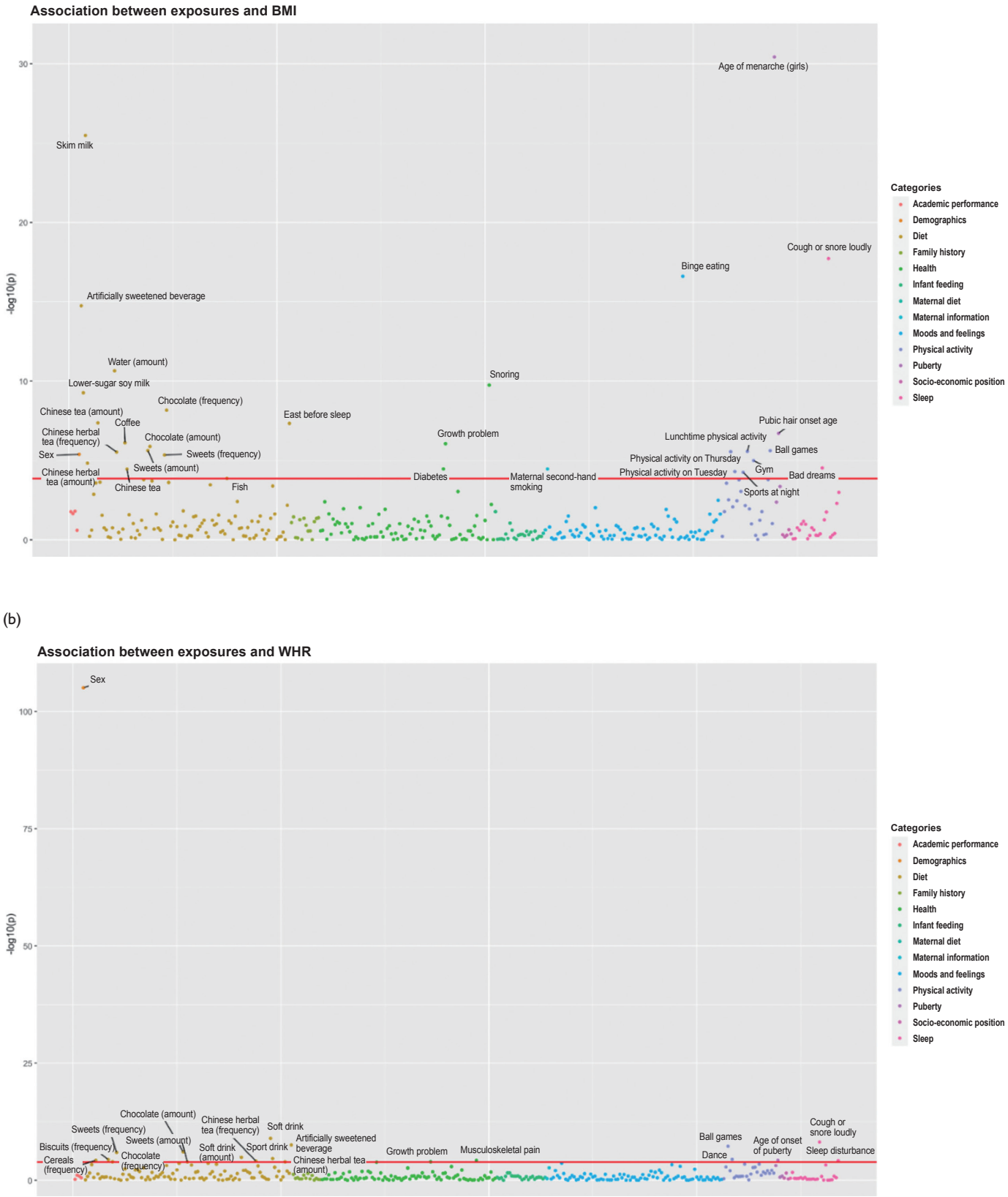

FIG 1. Associations of all exposures with (a) body mass index (BMI) and (b) waist-to-hip ratio (WHR) at age ~17.5 years among 3618 participants from the 'Children of 1997' birth cohort in the Biobank clinical follow-up. Cut-off lines indicate Bonferroni-corrected P value thresholds

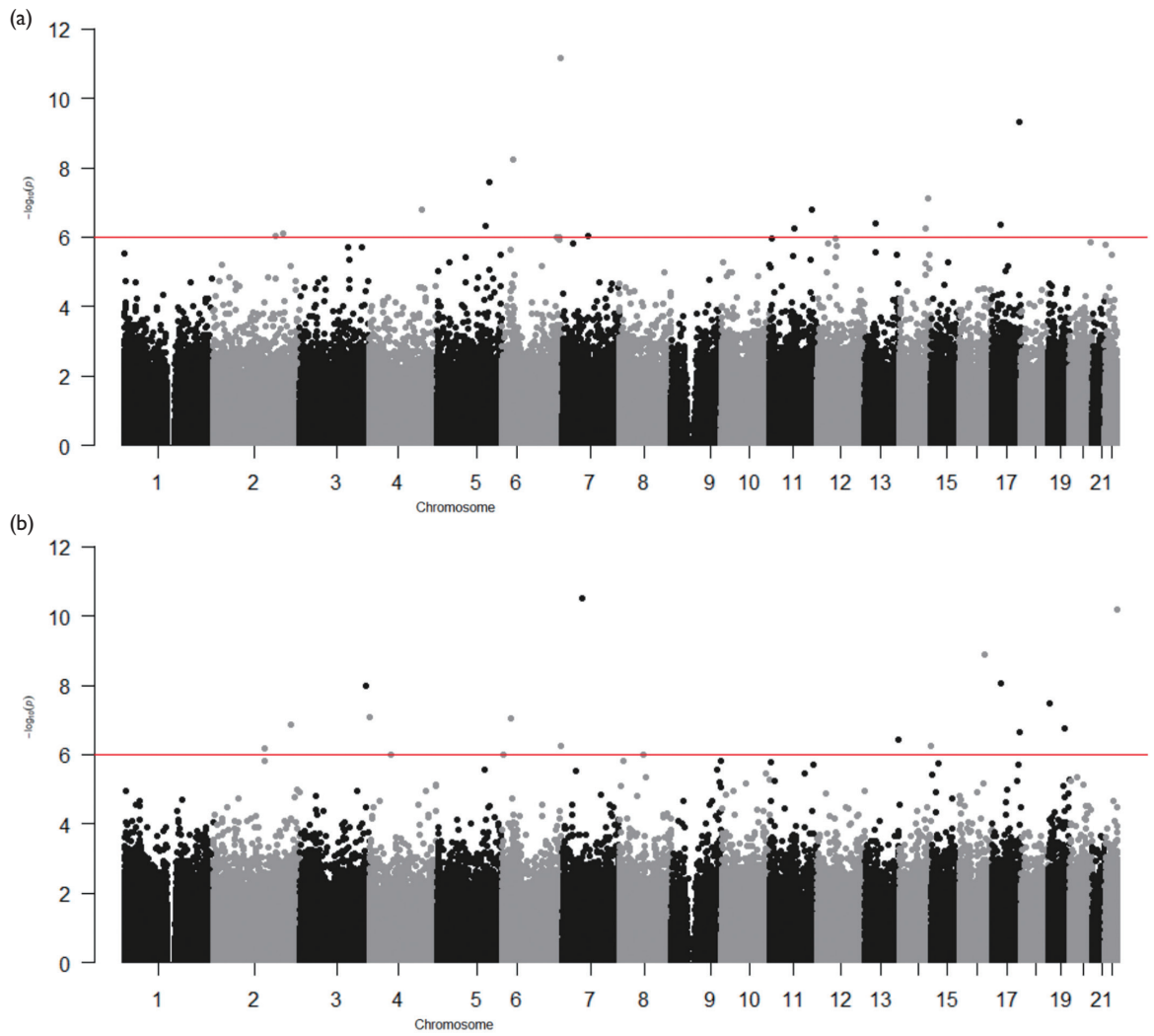

FIG 2. Epigenome-wide associations with (a) body mass index and (b) waist-to-hip ratio at age ~23 years among 286 participants from the 'Children of 1997' birth cohort in the follow-up survey

Genes *ZNF827*, *MIR7641-2*, *RPTOR*, *KSR1*, *GTF3C3*, and *NFIC* were associated with obesity or obesity-related disorders. *KSR1* is reportedly associated with the regulation of glucose homeostasis, and *GTF3C3* is reportedly associated with obesity-related dysglycaemia. *NFIC*, which encodes nuclear factor I-C, regulates adipocyte differentiation. *OPA3* is a novel regulator of mitochondrial function and controls thermogenesis and abdominal fat mass.

There are several limitations to the study. The sample sizes in the EWAS and epigenome-wide association study were relatively small. Results of the present study should be replicated in larger populations. The use of questionnaires to ascertain exposures is susceptible to recall bias and social desirability bias. Although level of confounding was minimal, residual confounding is likely to exist. Therefore, the associations are regarded as potential risk factors, rather than causal relationships.

Conclusions

Environmental exposures (eg, consumption of ASBs and binge eating) and epigenetics in early-life adiposity were associated with adiposity. If these associations are confirmed to be causal relationships, they may provide novel targets for interventions.

Funding

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Disclosure

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1. Zhao J, Fan B, Huang J, et al. Environment- and epigenome-wide association study of obesity in 'Children of 1997' birth cohort. Elife 2023;12:e82377.

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Serum microRNA test to identify individuals with high risk of colorectal cancer: abridged secondary publication

CC Foo *, CKH Wong, WL Law, CLK Lam, WK Leung, L Ng *

KEY MESSAGES

1. A serum microRNA test is a promising diagnostic biomarker for patients with colorectal cancer.
2. The combination of a serum microRNA test and colonoscopy is more cost-effective than colonoscopy alone.

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Introduction

Colorectal cancer (CRC) is the most common cancer in Hong Kong. In 2018, 5634 cases of CRC were newly diagnosed, accounting for 16.6% of all new cancer cases. CRC is the second most common cause of cancer-related death. In 2019, there were 2174 deaths from CRC, accounting for 14.6% of all cancer-related deaths.[1] CRC is curable if diagnosed at an early stage. Therefore, screening is particularly important in early detection of CRC.

Several serum miRNAs are promising biomarkers for CRC diagnosis, with individual area under the curve (AUC) values >0.800. We investigated the use of microRNAs (miRNAs) in blood to identify patients with CRC and compared cost-effectiveness between miRNA and conventional strategies for CRC screening.

Methods

Between 2017 and 2021, serum samples (3 mL each) were collected from patients with CRC and normal individuals at Queen Mary Hospital in Hong Kong. Respectively in the training set (stage 1) and validation set (stage 2), 129 and 200 pairs of normal individuals and patients with CRC were recruited. In the prediction set (stage 3), 105 normal individuals and 155 patients with CRC were recruited to determine the predictive value of miRNA panel (Table).

Serum miRNA was extracted. Total RNA was reverse transcribed to generate 20 µl of genomic DNA-free cDNA. Quantitative polymerase chain reaction (PCR) was performed.

Intergroup comparisons were conducted by *t* tests and Mann-Whitney *U* tests. Statistical

TABLE. Characteristics of normal individuals and patients with colorectal cancer (CRC) in three cohorts

	Training set		Validation set		Prediction set	
	Normal individuals (n=129)	Patients with CRC (n=129)	Normal individuals (n=200)	Patients with CRC (n=200)	Normal individuals (n=105)	Patients with CRC (n=155)
No. of men	40	59	84	135	49	101
No. of women	89	70	116	65	56	54
Age, y*	58.1±8.23	67.5±9.53	60.1±11.52	67.5±11.88	60.1±9.20	69.4±12.17

* Data are presented as mean ± standard deviation

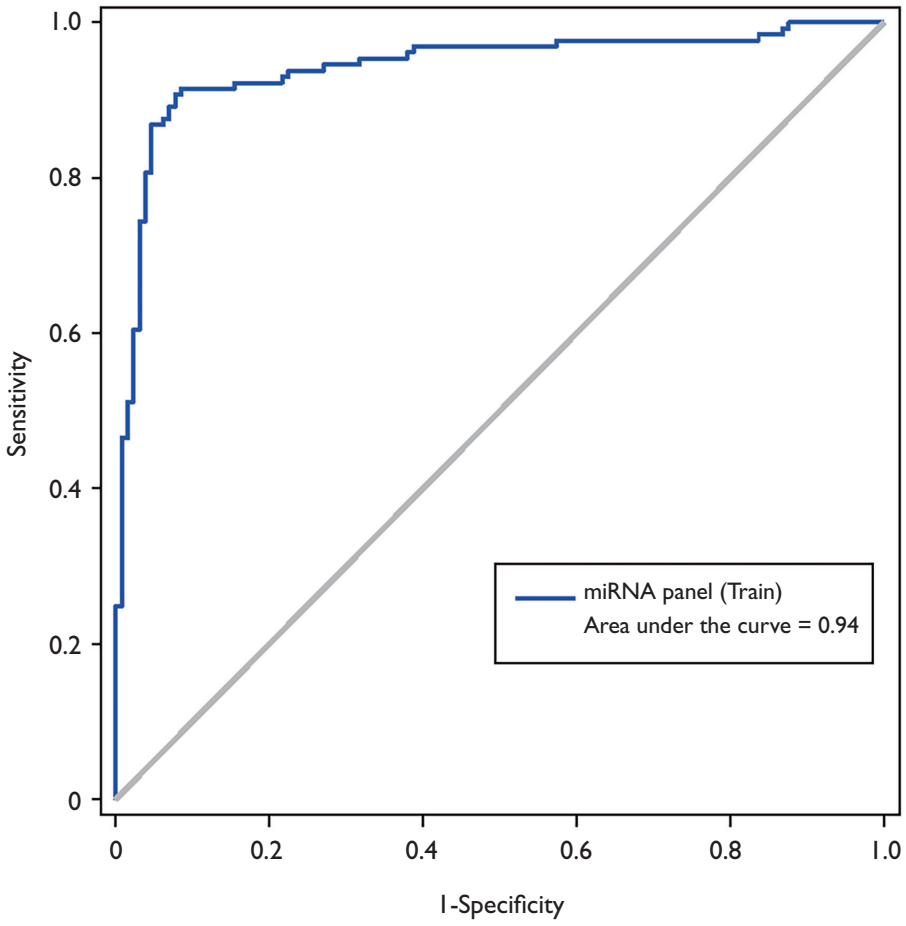

FIG 1. Diagnostic performance of the serum microRNA panel for identifying patients with colorectal cancer in the training set

analyses were conducted using SigmaPlot 10.0 (Systat Software, San Jose [CA], USA). A P value of <0.05 (two-tailed) was considered statistically significant.

We compared the costs of two CRC screening strategies: (1) colonoscopy alone and (2) miRNA panel followed by colonoscopy for miRNA panel–positive patients. The costs of the miRNA test and colonoscopy were determined based on the median costs in the private sector.

Results

We performed multiple linear regression to identify three miRNA pairs for CRC diagnosis: serum miRNA panel (Training) score = -0.35 + (0.0171 * miR-106b-5p/miR-1246) + (0.217 * miR-106b-5p/miR-16) – (0.133 * miR-106b-5p/miR-21-5p). The AUC of this miRNA panel for CRC diagnosis was 0.94 (P<0.0001, Fig 1).

The AUC of the miRNA panel (Training) for CRC diagnosis in the validation cohort was 0.77 (P<0.0001, Fig 2). The AUC, sensitivity, and specificity were all decreased compared with those values in the training cohort. Hence, we formulated a miRNA panel using data from patients in the validation cohort. The following formula was derived: serum miRNA panel (Validation) score = -0.32 + (0.0471 * miR-106b-5p/miR-1246) + (0.137 * miR-106b-5p/miR-16) + (0.0196 * miR-106b-5p/miR-21-5p). The AUC of this miRNA panel (Validation) for CRC diagnosis was 0.89 (P<0.0001, Fig 2).

We calculated the serum miRNA panel (Validation) score and used a cut-off value of 0.53 for prediction of CRC. Among 155 patients with CRC, 133 patients were correctly identified (sensitivity=85.8%), whereas 85 of 105 normal individuals were correctly identified (specificity=80.95%). The positive and negative predictive values were 86.9% and 79.4%, respectively.

The cost of colonoscopy at 12 private hospitals or medical centres ranged from $4050 to $14 060, and the median cost was $9910 (interquartile range, $8800-$10 610). The cost of the serum miRNA test

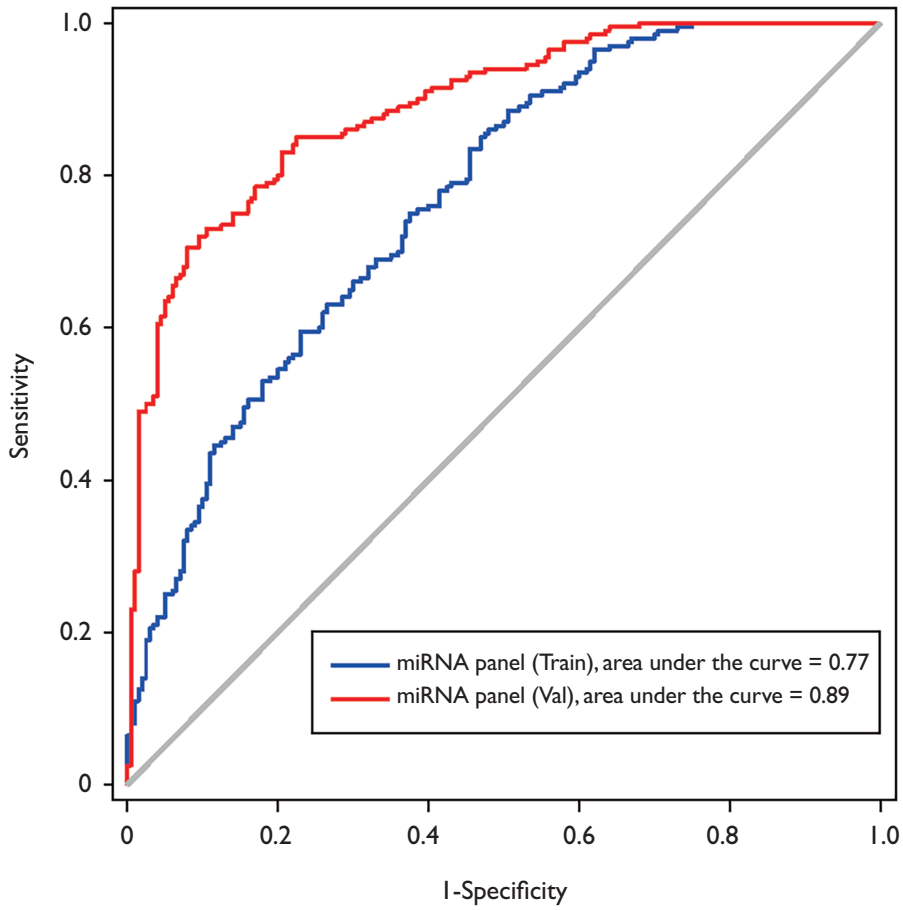

FIG 2. Diagnostic performance of the serum microRNA panel for identifying patients with colorectal cancer in the validation set

was based on the cost of a COVID-19 PCR test, which ranged from $240 to $2110 at 23 private medical centres, and the median cost was $1180 (interquartile range, $950-$1492.5). Between 2017 and 2021, annually on average, 114 patients with CRC and 1975 normal individuals underwent colonoscopy at Queen Mary Hospital.

The estimated CRC detection sensitivity of colonoscopy is 95%.[2] At this sensitivity, the specificity of the serum miRNA test was 52.38%. The cost of the serum miRNA test for all 2089 patients was $2 465 020 (2089 × $1180). Based on the 52.38% specificity of the serum miRNA test, 1094 normal individuals with a normal serum miRNA test result could avoid colonoscopy screening. The savings would be $10 841 540 (1094 × $9910). After subtracting the cost of the serum miRNA test ($10 841 540 – $2 465 020 = $8 376 520), the average cost savings per patient would be $4010 ($8 376 520 / 2089).

Discussion

The serum miRNA test is a promising diagnostic biomarker for patients with CRC. Moreover, a combination of a serum miRNA test and colonoscopy is more cost-effective than colonoscopy alone. The average cost savings per patient is approximately $4000. From 2017 to 2021, the total number of colonoscopies performed in all public hospitals was around 267 000. Assuming that the proportion of patients with CRC was similar to that in our hospital (52.8%), the number of patients with CRC in all public hospitals was 140 976. Hence, the cost savings using a combination of a serum miRNA test and colonoscopy would have been 564 million dollars.

There were limitations in this study. The samples were collected from patients recruited at a single hospital. Although we validated the findings in three different patient cohorts, the results would be more robust if our serum miRNA panel could perform consistently among patient

samples collected at other hospitals. In addition, the performance of the serum miRNA test in identifying patients with polyps was not evaluated.

Conclusions

The serum miRNA test is a promising diagnostic biomarker for identifying patients with CRC, with AUC around 0.9. A combination of a serum miRNA test and colonoscopy is more cost-effective than colonoscopy alone.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#04151956). The full report is available from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

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Four-dimensional diffusion-weighted magnetic resonance imaging for stereotactic body radiation therapy in patients with abdominal cancer: abridged secondary publication

J Cai *, T Li, HFV Lee, HC Chang

KEY MESSAGES

1. Compared with T1- and T2-weighted four-dimensional magnetic resonance imaging, four-dimensional diffusion-weighted imaging (4D-DWI) enables higher tumour contrast-to-noise ratio and hence highly consistent gross tumour volume contours and low interobserver errors.
2. A deep learning–based 4D-DWI yields significant improvements in image quality including tumour contrast-to-noise ratio and image texture.
3. In patients with abdominal cancer, 4D-DWI demonstrates high detectability with accurate tumour motion and tumour delineation.
4. 4D-DWI has potential to improve the accuracy of radiotherapy for mobile abdominal cancers and reduce radiation adverse effects.

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Introduction

Abdominal tumours are major causes of cancer-related death in Hong Kong and worldwide. Liver cancer and pancreatic cancer are the third and fourth leading causes of cancer-related death, respectively, in Hong Kong.[1] The role of radiotherapy in abdominal tumour management is limited owing to radiation toxicity in non-target tissues. Stereotactic body radiation therapy (SBRT) has been used for management of early-stage abdominal tumours because it enables delivery of high-dose conformal radiotherapy with limited toxicity. Respiratory motion (can be up to 4 cm) is a major obstacle to achieving more effective SBRT for abdominal tumours.[2] Four-dimensional (4D) imaging plays an essential role in the management of tumour motion:[2] 4D computed tomography (CT) is ineffective for abdominal tumours owing to its low soft-tissue contrast, whereas 4D magnetic resonance imaging (MRI) exhibits superior soft-tissue contrast but suboptimal and inconsistent tumour contrast.[3,4] We therefore developed a novel 4D diffusion-weighted imaging (DWI) technique.[5] It has high tumour contrast-to-noise ratio (CNR) and does not require exogenous contrast medium. We aimed to evaluate the efficacy of 4D-DWI for treatment planning in patients with abdominal tumours.

Methods

We included 36 patients with abdominal tumour(s) in the liver or pancreas and four healthy volunteers. We developed and validated a robust sorting method based on anatomical features to improve image quality in 4D-MRI. We then developed the retrospective motion artefact suppression by synthetic radial k-space (R-MASSK), which can be integrated into the clinical 4D-MRI workflow to suppress motion artefacts and enhance image quality through simulated k-space resampling. We then developed a new (K-B-optimised) binning method to address the need for propeller reconstruction when sorting the blade data, thereby improving the k-space distribution. This method is intended to resolve an issue of 4D-DWI, in which amplitude data binning with continuous intervals to sort blade data could lead to non-uniform k-space sampling, leading to suboptimal results in subsequent reconstruction. We then developed a deep learning–based deformable image registration method—dual-supervised deformation estimation model—to improve 4D-MRI

image quality including 4D-DWI. We evaluated the efficacy of 4D-DWI in radiotherapy planning in terms of tumour CNR, gross tumour volume (GTV) dice similarity coefficient (DSC), and tumour motion error.

Results

4D-MRI based on anatomic feature matching was able to improve image quality by reducing breathing-induced motion image artefacts. The R-MASSK method was capable of suppressing motion artefacts and enhancing the quality of clinically acquired 4D-MRI. The K-B-optimised binning method effectively improved the robustness of 4D-DW-propeller echo-planar imaging.

Our deep learning–based method of synthesising ultra-quality multiparametric 4D-MRI (including 4D-DWI) showed accurate tumour motion trajectory and significantly better image quality, compared with conventional 4D-MRI.

The tumour CNR increased from 8.30±6.87 in 4D-MRI to 8.66±6.46, 22.49±21.54, 35.28±35.29, and 29.81±24.36 in T1-weighted 4D-MRI, T2-weighted 4D-MRI, 4D-DWI (b=50), and 4D-DWI (b=800), respectively. 4D-DWI enables higher tumour CNR. Reconstructed images in the sagittal view from a sample patient are shown in Fig 1.

Respectively in the superior-inferior, anterior-posterior, and medial-lateral directions, the relative motion errors were 1.12±0.89 mm, 0.51±0.39 mm,

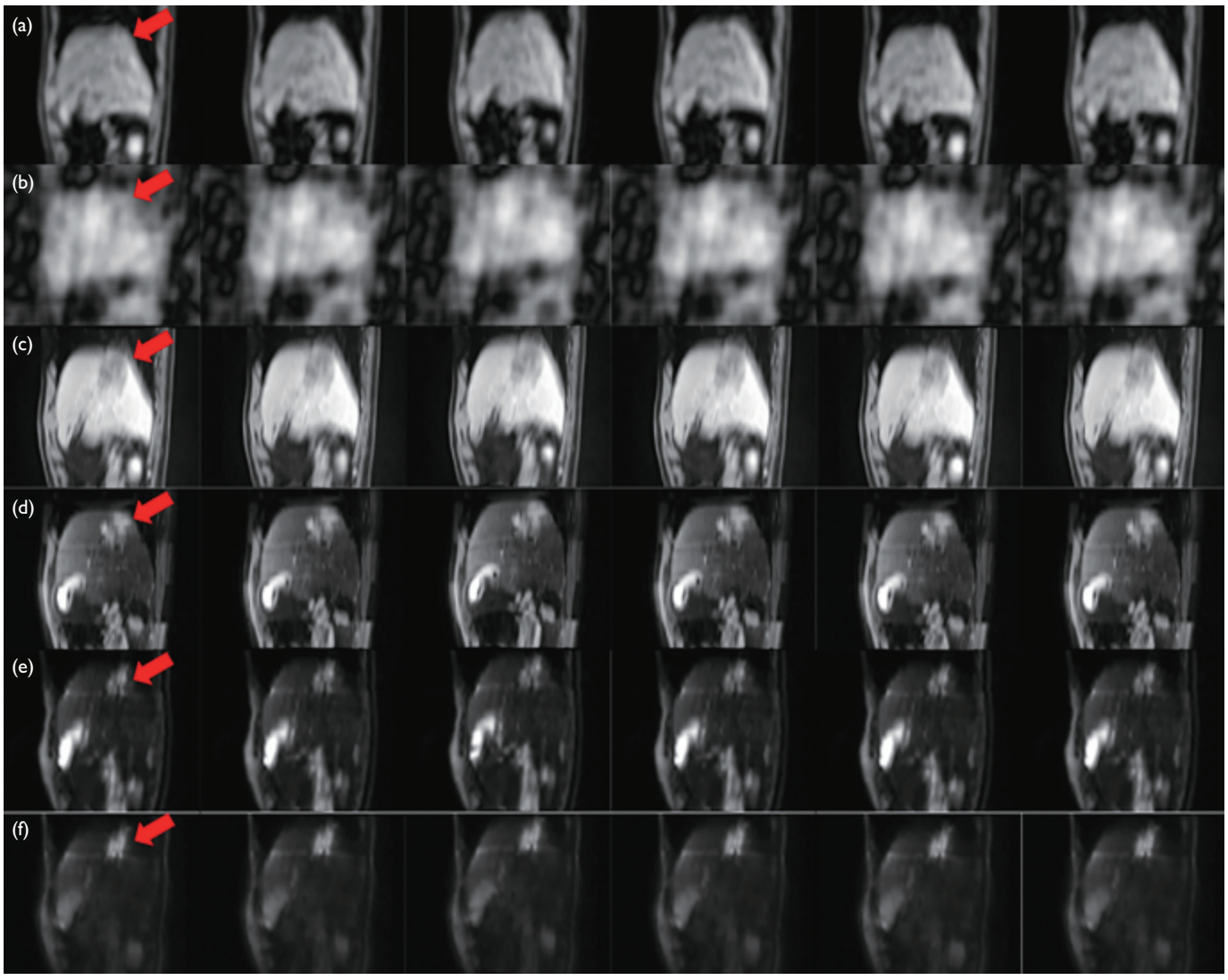


FIG 1. Reconstructed images in the sagittal view from a sample patient: (a) original four-dimensional (4D) magnetic resonance imaging (MRI), (b) downsampled 4D-MRI, (c) T1-weighted 4D-MRI, (d) T2-weighted 4D-MRI, (e) 4D-diffusion-weighted imaging (DWI) [b=50], and (f) 4D-DWI (b=800)

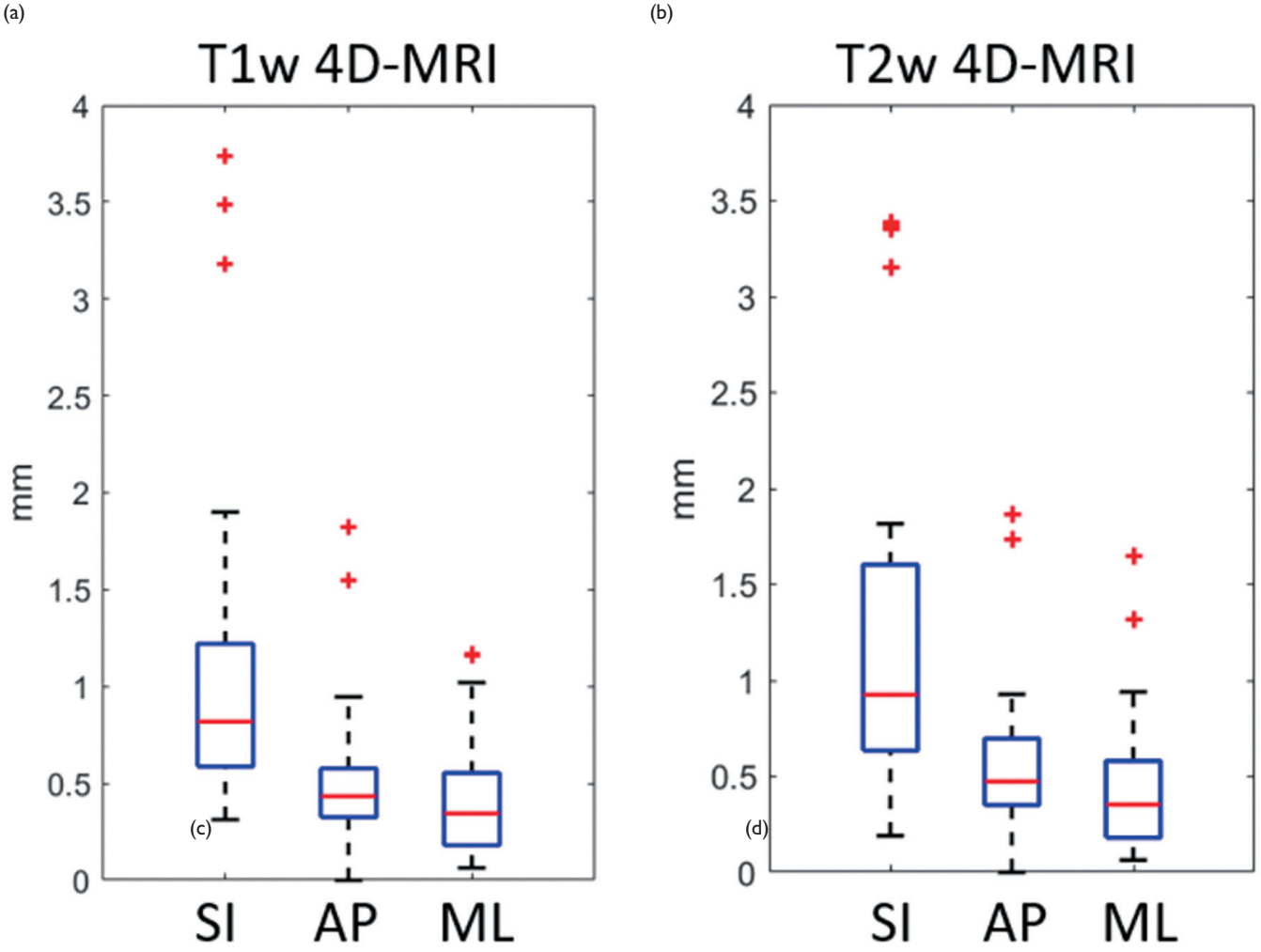


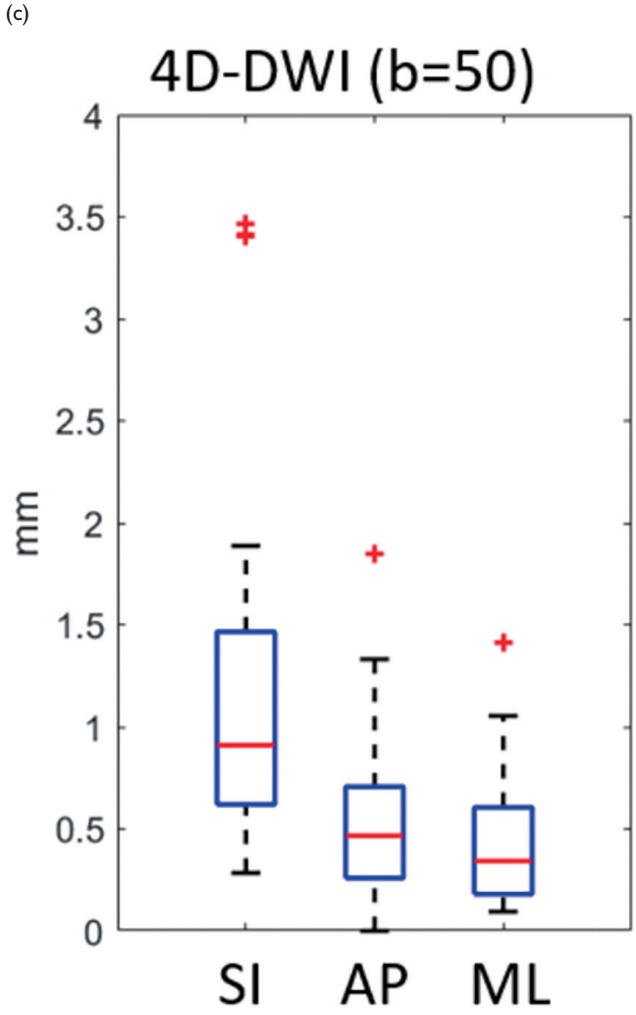
FIG 2. Relative motion errors in the superior-inferior (SI), anterior-posterior (AP), and medial-lateral (ML) directions of (a) T1-weighted four-dimensional (4D) magnetic resonance imaging (MRI), (b) T2-weighted 4D-MRI, (c) 4D diffusion-weighted imaging (DWI) [b=50], and (d) 4D-DWI (b=800)

and 0.41±0.31 mm in T1-weighted 4D-MRI; 1.24±0.93 mm, 0.55±0.39 mm, and 0.45±0.38 mm in T2-weighted 4D-MRI; 1.21±0.86 mm, 0.51±0.37 mm, and 0.42±0.32 mm in 4D-DWI (b=50); and 1.15±0.82 mm, 0.52±0.38 mm, and 0.38±0.28 mm in 4D-DWI (b=800) [Fig 2].

Respectively in 4D-CT, T1-weighted 4D-MRI portal-venous phase, T2-weighted 4D-MRI, 4D-DWI, T1-weighted 4D-MRI delayed phase, and fused 4D-MRI, the interobserver means of the GTV DSC values were 0.81±0.09, 0.85±0.08, 0.88±0.04, 0.89±0.08, 0.90±0.04, and 0.95±0.02, whereas the inter-patient coefficients of variation of the DSC were 11.8%, 9.3%, 5.1%, 8.5%, 4.6%, and 2.4%. 4D-DWI resulted in highly consistent GTV contours and low interobserver errors (Fig 3).

Discussion

The visualisation of tumours and their motion is critical for tumour delineation, and 4D-DWI has high potential for precise management of tumour motion during radiotherapy. A robust sorting method based on anatomic feature matching largely reduces breathing-induced artefacts. It directly preserves organ/tissue structures by aligning or matching them in two groups of orthogonal images. The method uses external breathing signals to guide the sorting or reconstruction procedure, thereby requiring additional synchronisation and correlation



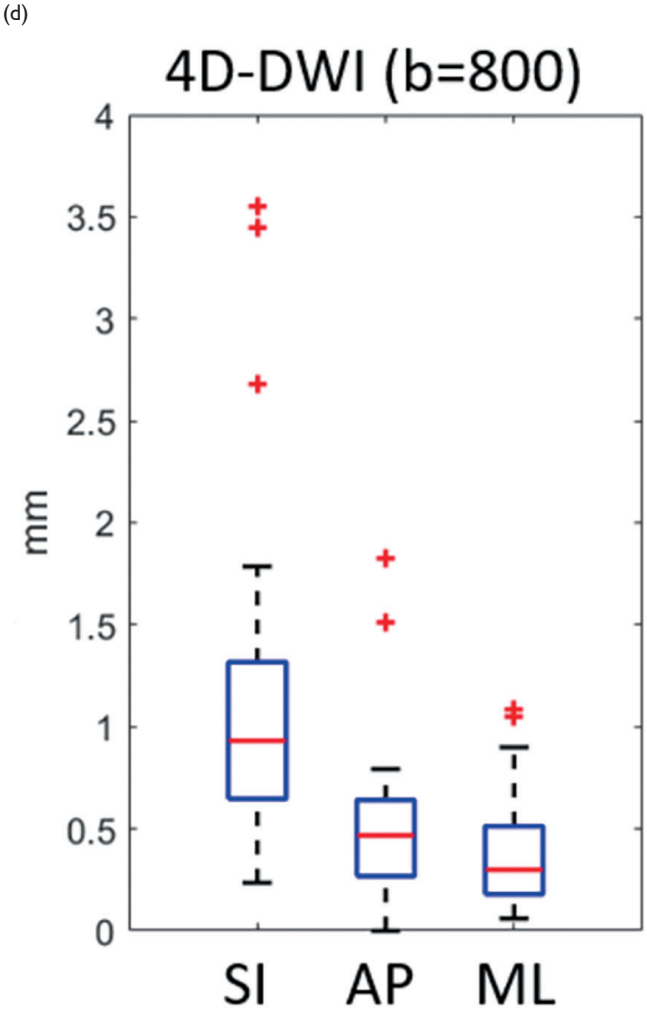


FIG 2. (cont'd)

of the scans and breathing signals. Our new sorting method utilises changes in anatomic features across images to form bins and guide the sorting process, leading to better validity and accuracy.

The deep learning–based method led to significant improvements in image quality including tumour CNR and image texture. Deep learning-based 4D-DWI has advantages over conventional 4D-MRI, which relies on sorting algorithms and is thus vulnerable to irregular breathing and can cause stitching artefacts or missing slices. Furthermore, the spatial resolution of existing methods is often compromised owing to the time efficiency and data sufficiency requirements of 4D-MRI. Existing methods also have long acquisition times.

Conclusions

The 4D-DWI technique is effective for accurately measuring tumour respiratory motion and delineating target volume in patients with abdominal cancer. It has high tumour CNR and minimal interobserver variability. This indicates that the detectability and accuracy of tumour motion and tumour delineation are better in 4D-DWI than in other types of 4D-MRI.

Funding

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong SAR Government (#06173276). The full report is available

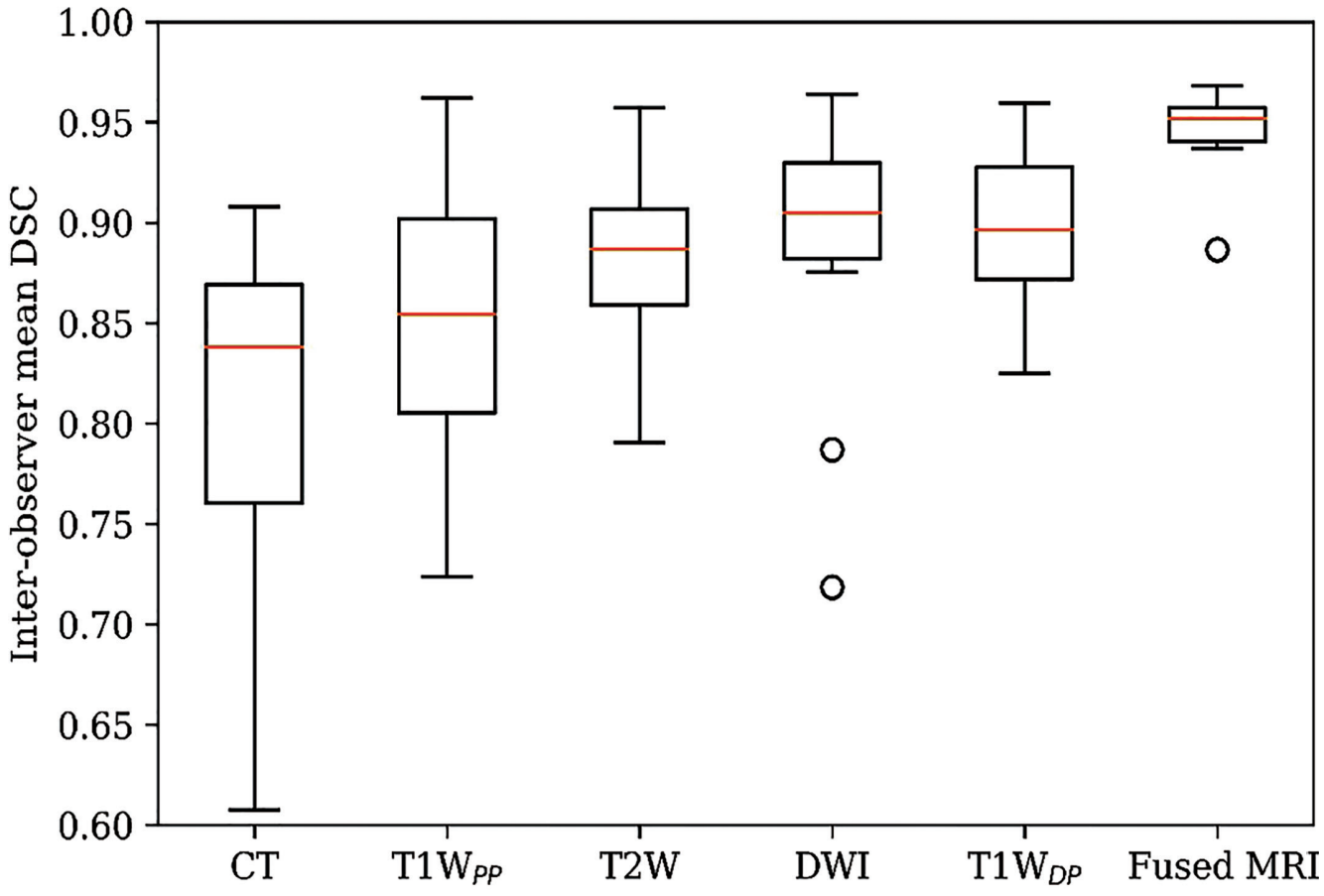


FIG 3. Interobserver means of gross tumour volume dice similarity coefficient (DSC) in computed tomography (CT) and various magnetic resonance imaging (MRI) sequences: T1-weighted portal-venous phase (T1W$_{PP}$), T2-weighted (T2W), diffusion-weighted imaging (DWI), T1-weighted delayed phase (T1W$_{DP}$), and fused MRI among patients with liver cancer.

from the Health and Medical Research Fund website (https://rfs2.healthbureau.gov.hk).

Disclosure

The results of this research have been previously published in:

1. Yang Z, Ren L, Yin FF, Liang X, Cai J. Motion robust 4D-MRI sorting based on anatomic feature matching: a digital phantom simulation study. Radiat Med Prot 2020;1:41-7.
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Gut microbiota across early stages of synucleinopathy: abridged secondary publication

YK Wing *, J Zhang, KF To, CTV Mok, SMS Ng, HS Wong, XS Li

KEY MESSAGES

1. Gut dysbiosis is present in individuals with early and prodromal stages of synucleinopathy, including patients with rapid eye movement sleep behaviour disorder and their first-degree relatives who exhibit earlier prodromal features of the disorder.
2. Gut microbiome features might be a promising target for the early prevention and treatment of synucleinopathy.

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HMRF project number: 05162876

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Introduction

Synucleinopathies, such as Parkinson's disease (PD), are characterised by the abnormal aggregation of alpha-synuclein protein in the central nervous system. However, there is increasing evidence that alpha-synuclein pathology occurs in the enteric nervous system prior to central nervous system, which strongly supports the gut-to-brain propagation of synucleinopathy. In parallel, gut microbiota disturbance (gut dysbiosis), an emerging biomarker and treatment target for various complex diseases, has been consistently reported in patients with PD.[1] It is hypothesised that PD-associated gut dysbiosis, especially the depletion of short-chain fatty acid (SCFA)–producing bacteria and enrichment of putative pathobionts, is related to intestinal hyperpermeability, immune activation, and pathological alpha-synuclein aggregation.

Rapid eye movement sleep behaviour disorder (RBD) is the most specific prodromal marker of PD. Patients with RBD display an increased prevalence of constipation, along with increased immunostaining of phosphorylated alpha-synuclein in the enteric nervous system. Additionally, a recent case-control-family study reported that the first-degree relatives of patients with RBD (RBD-FDR) had increased constipation and a range of RBD features: from isolated RBD symptoms (indicative of prodromal RBD) to video polysomnography–diagnosed RBD. Therefore, RBD-FDR might comprise a group of susceptible individuals at a much earlier stage of synucleinopathy, compared with patients with RBD.[2]

We performed a large cross-sectional study across various early stages of disease to identify the associations of gut microbiota with the progression of synucleinopathy.

Methods

We recruited four groups of individuals representing different stages of PD: patients with PD but without dementia, patients with RBD, RBD-FDR, and healthy controls (Fig 1). Their sociodemographics, lifestyle, excessive daytime sleepiness, autonomic function, and RBD features were recorded with a comprehensive questionnaire, as were psychiatric disorders, motor dysfunction, orthostatic hypotension, olfactory function, and dementia. Bowel disorders, such as functional constipation, were diagnosed using the Rome IV diagnostic questionnaire.

Fresh stool samples were frozen at -80°C within 4 hours of collection. DNA extraction was performed using the DNeasy PowerSoil Pro DNA Kit (Qiagen). DNA libraries were constructed using primers spanning the targeted V3-V4 hypervariable regions of 16S ribosomal RNA genes.

Univariate analyses of categorical data were performed using the Chi-squared test or Fisher's exact test. For continuous data with a normal distribution, analysis of variance was performed

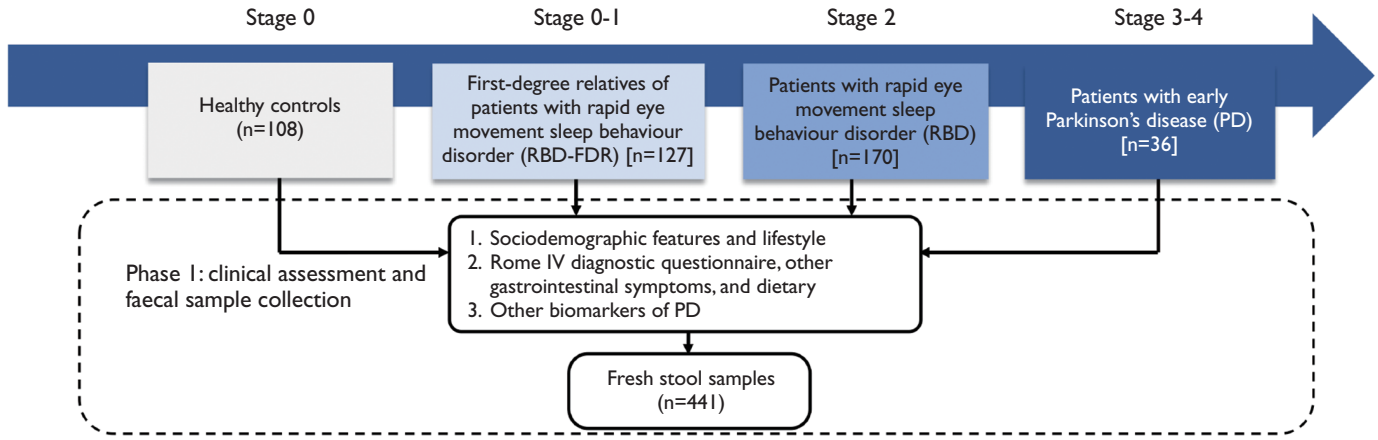


FIG 1. Flowchart of the study

followed by a post hoc test; otherwise, the Kruskal-Wallis H test was used. Considering potential associations between participants from the same family, a generalised estimating equation model was used to adjust for family clustering.[2] A two-sided P value of <0.05 was considered statistically significant. Compositional differences between each pair of groups were analysed using permutational multivariate analysis of variance (PERMANOVA) and then visualised using principal coordinates analysis. Differential taxa between groups were identified using the Kruskal-Wallis test with post hoc analysis. Correlations of significantly different faecal microbiota and host factors were assessed using microbiome multivariable associations with linear model. For multiple comparisons, P values were adjusted using the Benjamini-Hochberg false discovery rate, and a false positive rate of <5% (q<0.05) was considered statistical significance.

Results

With additional funding from the Faculty of Medicine, the Chinese University of Hong Kong, the proposed sample size (36 participants per arm) was increased to 108 controls, 127 RBD-FDR, 170 patients with RBD, and 36 patients with early PD.[3] Age and sex were comparable among controls (67.3 years, 63.9% men), patients with RBD (68.6 years, 73.5% men), and patients with early PD (67.8 years, 86.1% men), but the RBD-FDR group (58.0 years, 48.8% men) was younger and comprised more women, compared with controls (q<0.001). The prevalence of functional constipation showed an increasing trend across groups: from controls to RBD-FDR to patients with RBD to patients with early PD (8.3% vs 9.4% vs 45.3% vs 69.4%, P<0.001, Tables 1 and 2).

Faecal microbiome analysis showed that the early PD group displayed a distinct microbiota clustering pattern, compared with controls (R^2=0.035, q<0.001).[3] The RBD group was similar to the early PD group (R^2=0.0081, q=0.07) but differed from the control and RBD-FDR groups (all q<0.001, Fig 2). The RBD-FDR and control groups did not differ significantly. Differential taxa analysis revealed that SCFA-producing bacteria (eg, *Roseburia, Lachnospiraceae_ND3007_group*, *Lachnospira, [Eubacterium]_ventriosum_group*, *Butyricicoccus, Faecalibacterium, and Lachnospiraceae*), hydrogen sulphide-producing *Desulfovibrio*, mucin-degrading *Akkermansia*, *Collinsella*, *UBA1819*, and *Oscillospiraceae_UCG-002* and *-005*) were significantly (and similarly) altered in RBD and early PD groups, compared with controls (all q<0.05). Notably, the enrichment of pro-inflammatory *Collinsella* occurred in RBD-FDR, an early stage of synucleinopathy (adjusted (β=0.58, q=0.035).[3]

Correlations of differential microbe abundance with clinical biomarkers of synucleinopathy were explored. Genus *UBA1819* was associated with olfactory impairment (*r*=0.15, P=0.004), constipation/bowel movement frequency (*r*=0.32, P<0.001), and total likelihood ratio of prodromal PD (*r*=0.22, P<0.001). Among faecal samples, gut microbes enriched in early synucleinopathy (eg, *Desulfovibrio, Akkermansia, UBA1819, Family_XIII_AD3011_group*, and *Oscillospiraceae_UCG-005*) were positively correlated with cognitive decline and motor dysfunction, whereas microbes

TABLE 1. Sociodemographic, gastrointestinal, and clinical characteristics of participants (permission from: Huang B, Chau SWH, Liu Y, et al. Gut microbiome dysbiosis across early Parkinson's disease, REM sleep behavior disorder and their first-degree relatives. Nat Commun 2023;14:2501)

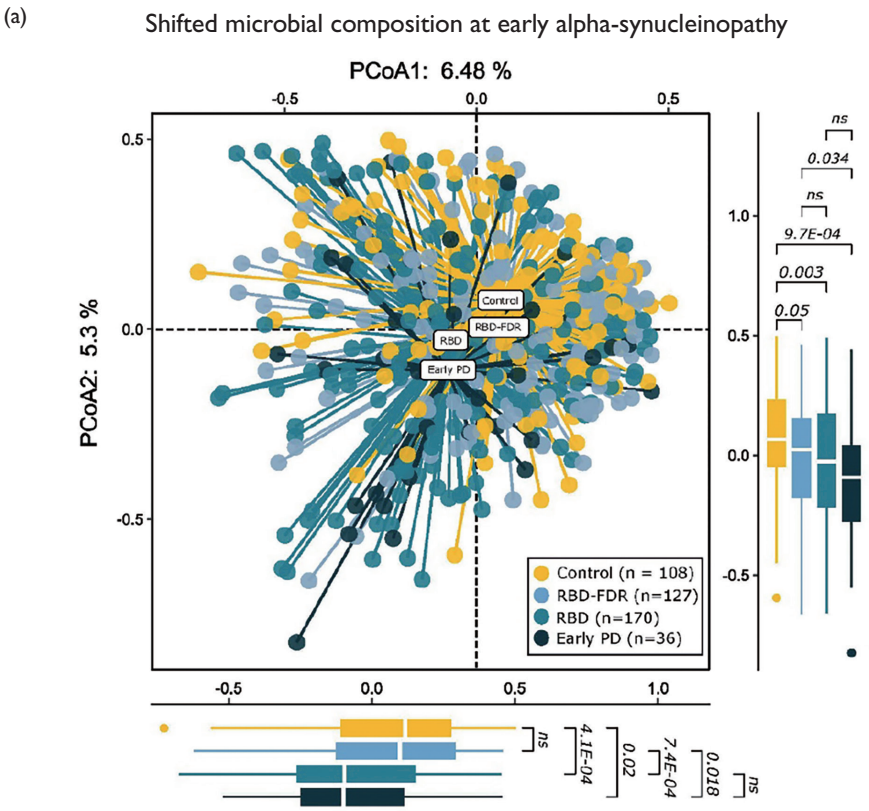
Characteristic	Healthy controls (n=108)*	First-degree relatives of patients with rapid eye movement sleep behaviour disorder (RBD-FDR) [n=127]*	Patients with rapid eye movement sleep behaviour disorder (RBD) [n=170]*	Patients with early Parkinson's disease (PD) [n=36]*	P value	Post hoc analysis
Age, y	67.3±7.0	58.0±9.5	68.6±7.6	67.8±5.6	<0.001	RBD-FDR<control=RBD=PD
Male sex	69 (63.9)	62 (48.8)	125 (73.5)	31 (86.1)	<0.001	RBD-FDR<control=RBD=PD
Body mass index, kg/m^2	24.8±3.7	24.4±3.1	24.5±3.7	24.5±2.7	0.94	-
Comorbidities						
Cardiovascular disease	16 (14.8)	7 (5.7)	33 (19.4)	5 (13.9)	0.19	-
Diabetes, type 2	15 (13.9)	19 (15.0)	28 (16.5)	5 (13.9)	0.30	-
Dyslipidaemia	36 (33.3)	39 (30.7)	54 (31.8)	13 (36.1)	0.51	-
Fatty liver	4 (3.7)	14 (11.0)	10 (5.9)	2 (5.6)	0.98	-
Depression, lifetime	15 (13.9)	28 (22.0)	54 (31.8)	10 (27.8)	<0.001	control=RBD-FDR<RBD=PD
Anxiety disorder, lifetime	5 (4.6)	14 (11.0)	34 (20.0)	5 (13.9)	0.001	control=RBD-FDR<RBD
Gout	2 (1.9)	5 (3.9)	14 (8.2)	2 (5.6)	0.31	-
Medications						
Proton pump inhibitors	8 (7.4)	8 (6.3)	21 (12.4)	2 (5.6)	0.51	-
Statins	26 (24.1)	18 (14.2)	58 (34.1)	5 (13.9)	0.12	-
Osmotic laxatives	1 (0.9)	2 (1.6)	9 (5.3)	11 (30.6)	<0.001	control=RBD-FDR=RBD<PD
Beta blockers	11 (10.2)	5 (3.9)	13 (7.6)	6 (16.7)	0.19	-
Antidepressants	5 (4.6)	6 (4.7)	43 (25.3)	5 (13.9)	<0.001	control=RBD-FDR<RBD
Benzodiazepines	2 (1.9)	4 (3.1)	99 (58.2)	21 (58.3)	<0.001	control=RBD-FDR<RBD=PD
Metformin	7 (6.5)	11 (8.7)	18 (10.6)	3 (8.3)	0.42	-
Urate-lowering drugs	2 (1.9)	1 (0.8)	6 (3.5)	0	0.78	-
Supplements						
Vitamin	13 (12.6)	16 (13.4)	25 (15.3)	6 (17.1)	0.58	-
Calcium	13 (12.6)	13 (10.9)	25 (15.3)	6 (17.1)	0.13	-
Probiotics, ≥1 time/week	17 (15.7)	13 (10.2)	24 (14.1)	7 (19.4)	0.11	-
Prebiotics, ≥1 time/week	2 (1.9)	6 (4.7)	13 (7.6)	2 (5.6)	0.12	-
Rapid eye movement sleep behaviour disorder questionnaire–Hong Kong	6.3±7.0	9.2±8.4	39.2±17.7	32.8±16.1	<0.001	control=RBD-FDR<RBD=PD
Factor 1	4.8±4.4	6.1±4.7	13.3±6.3	11.1±5.8	<0.001	control=RBD-FDR<RBD=PD
Factor 2	1.5±3.8	3.1±5.4	25.9±12.7	21.7±12.0	<0.001	control<RBD-FDR<RBD=PD
Rome IV diagnostic questionnaire for adult functional gastrointestinal disorders						
Functional constipation	9 (8.3)	12 (9.4)	77 (45.3)	25 (69.4)	<0.001	control=RBD-FDR<RBD<PD
Straining with defecation, ≥50% bowel movement	9 (8.8)	19 (15.8)	74 (45.4)	24 (68.6)	<0.001	control<RBD-FDR<RBD<PD
Incomplete evacuation, ≥50% bowel movement	14 (13.7)	15 (12.5)	51 (31.3)	13 (38.2)	0.001	control=RBD-FDR<RBD=PD
Anorectal obstruction/blockage, ≥40% bowel movement	14 (14.0)	10 (8.3)	52 (32.1)	13 (38.2)	<0.001	control=RBD-FDR<RBD=PD
Manual manoeuvres, ≥20% bowel movement	9 (8.8)	18 (15.0)	51 (31.3)	14 (41.2)	0.001	control=RBD-FDR<RBD=PD
Irritable bowel syndrome	2 (1.9)	6 (5.0)	6 (3.6)	1 (2.8)	0.60	-
Functional diarrhoea	7 (6.5)	7 (5.8)	7 (4.2)	0	0.44	-
Bowel movement frequency score	2.0±0.81	2.1±0.70	2.7±1.0	3.4±1.2	<0.001	control=RBD-FDR<RBD<PD
Reversed Bristol Stool Form Scale	2.9±1.0	3.1±1.1	3.8±1.4	4.4±1.1	<0.001	control=RBD-FDR<RBD<PD
Scales for Outcomes in Parkinson's Disease–Autonomic						
Swallowing/choking, 1st item ≥2	16 (15.1)	21 (16.5)	39 (23.9)	8 (22.9)	0.58	-
Sialorrhea, 2nd item ≥2	3 (2.8)	1 (0.8)	9 (5.5)	4 (11.8)	0.07	-
Early satiety, 4th item ≥2	7 (6.7)	11 (8.7)	11 (6.7)	3 (8.8)	0.89	-

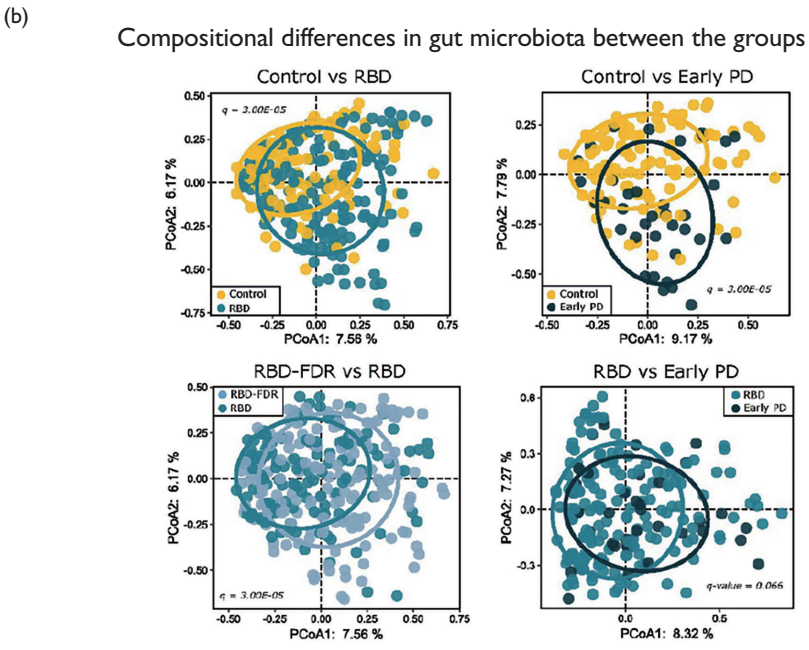
* Data are presented as mean ± standard deviation or No. (%) of participants

TABLE 2. Risk factors and prodromal markers of neurodegenerative diseases (permission from: Huang B, Chau SWH, Liu Y, et al. Gut microbiome dysbiosis across early Parkinson's disease, REM sleep behavior disorder and their first-degree relatives. Nat Commun 2023;14:2501)

Risk factor and prodromal marker	Healthy controls (n=108)*	First-degree relatives of patients with rapid eye movement sleep behaviour disorder (RBD-FDR) [n=127]*	Patients with rapid eye movement sleep behaviour disorder (RBD) [n=170]*	Patients with early Parkinson's disease (PD) [n=36]*	P value	Post hoc analysis
Male sex	69 (63.9)	62 (48.8)	125 (73.5)	31 (86.1)	<0.001	RBD-FDR<control=RBD=PD
Regular pesticide exposure	10 (8.5)	4 (3.3)	12 (7.1)	3 (8.3)	0.54	-
Consumption of caffeinated beverage ≤3 times/week	42 (35.3)	42 (34.1)	63 (37.3)	15 (42.9)	0.68	-
First-degree relative with Parkinson's disease	2 (1.9)	32 (25.2)	11 (6.5)	5 (13.9)	0.002	control=RBD<RBD-FDR, control<PD
Diabetes, type 2	15 (13.9)	19 (15.0)	28 (16.5)	5 (13.9)	0.30	-
Moderate to vigorous physical activity <1 hour/week	33 (33.7)	52 (42.6)	70 (42.4)	10 (27.8)	0.24	-
Smoking status						
Never	89 (84.0)	101 (80.2)	121 (72.5)	25 (69.4)	0.32	-
Former	11 (10.4)	15 (11.9)	32 (19.2)	10 (27.8)	0.03	control=RBD-FDR=RBD=PD
Current	6 (5.7)	10 (7.9)	14 (8.4)	1 (2.8)	0.36	-
Unified Parkinson's Disease Rating Scale part III score excluding action tremor	3.6±3.9	2.9±3.9	5.6±6.7	22.7±11.6	<0.001	control<RBD<PD
Olfactory impairment, Olfactory Identification test <3	21 (21.0)	20 (16.0)	108 (74.5)	29 (85.3)	<0.001	control=RBD-FDR<RBD=PD
Excessive daytime somnolence, Epworth sleepiness Score ≥14	19 (17.8)	23 (18.1)	32 (19.3)	5 (13.9)	0.80	-
Orthostatic hypotension	1 (0.9)	0	11 (6.5)	2 (5.6)	0.002	RBD-FDR<RBD
Erectile dysfunction, male only	14 (21.9)	6 (10.0)	45 (42.9)	13 (50.0)	0.007	control=RBD-FDR<RBD=PD
Urinary dysfunction	6 (5.7)	5 (3.9)	17 (10.3)	4 (11.4)	0.54	-
Depression, lifetime	15 (13.9)	28 (22.0)	54 (31.8)	10 (27.8)	<0.001	control=RBD-FDR<RBD=PD
Anxiety disorder, lifetime	5 (4.6)	14 (11.0)	34 (20.0)	5 (13.9)	0.001	control=RBD-FDR<RBD
Hong Kong version of Montreal Cognitive Assessment score	25.6±3.1	26.8±2.5	25.4±2.8	24.8±3.0	0.50	-
Farnsworth–Munsell 100 hue test, total error score	176.8±89.8	144.5±62.9	194.5±85.2	194.5±89.4	0.37	-
Total estimated likelihood ratio with log transformation	0.58±0.72	0.46±0.55	1.4±0.98	-	<0.001	control=RBD-FDR<RBD
Probable prodromal Parkinson's disease (>80%)	6 (5.6)	2 (1.6)	32 (18.8)	-	<0.001	control=RBD-FDR<RBD
Possible prodromal Parkinson's disease (30%-80%)	12 (11.1)	6 (4.7)	48 (28.2)	-	<0.001	control=RBD-FDR<RBD

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





Pairwise PERMANOVA tests

	Control		RBD		Early PD	
	R^2	*q-value*	R^2	*q-value*	R^2	*q-value*
Control	0.0075	0.060	0.017	**3.0E-05**	0.035	**3.0E-05**
RBD-FDR	/	/	0.016	**3.0E-05**	0.030	**3.0E-05**
RBD	/	/	/	/	0.008	0.066

FIG 2. (a) Faecal microbial composition across early stages of synucleinopathy, and (b) compositional differences in gut microbiota between groups (permission from: Huang B, Chau SWH, Liu Y, et al. Gut microbiome dysbiosis across early Parkinson's disease, REM sleep behavior disorder and their first-degree relatives. Nat Commun 2023;14:2501)
Abbreviations: RBD=rapid eye movement sleep behaviour disorder, RBD-FDR=first-degree relatives of patients with RBD, PD=Parkinson's disease, PERMANOVA=permutational multivariate analysis of variance

enriched in controls (eg, SCFA-producing bacteria *Faecalibacterium*, *Roseburia*, and *Lachnospiraceae_ND3007_group*) showed opposite correlations.

Discussion

Faecal microbiota communities in RBD-FDR, patients with RBD, and patients with early PD differed significantly from those communities in controls. The overall microbiota composition was similar in patients with RBD and patients with early PD, including depletion of SCFA-producing bacteria, and overabundance of *Collinsella*, *Desulfovibrio*, and *Oscillospiraceae UCG-005*. In RBD-FDR, comprising a younger population with an even earlier prodromal stage, there were emerging RBD/PD-like microbial changes, including an increase in pro-inflammatory *Collinsella* and a decrease in butyrate-producing *[Eubacterium]_ventriosum_group*.[3] Gut dysbiosis and enteric alpha-synuclein pathology were present at a much earlier stage, preceding the onset of RBD and PD. These findings highlight the critical role of the brain-gut-microbiota axis in the pathogenesis of synucleinopathy and provide a foundation for future research of specific gut microbes for the prevention of PD.

Gut dysbiosis occurred in the preclinical prodromal stages (RBD and RBD-FDR) of PD. Microbial community shifts were already present in patients with RBD, consistent with prior findings in patients with video polysomnography–diagnosed RBD and patients with possible RBD defined by a screening questionnaire.[4,5] PD-like gut dysbiosis—depletion of SCFA-producing bacteria—occurred prior to prodromal PD. Short-chain fatty acids, especially butyrate, are used as a source of energy by colonic epithelial cells; they modulate tight junctions between adjacent epithelial cells. The depletion of SCFA-producing bacteria may disrupt the integrity of the intestinal barrier, thereby contributing to intestinal hyperpermeability, activation of the enteric immune response, and subsequent aggregation of enteric alpha-synuclein. Furthermore, certain gut microbes (eg, *Collinsella* and *Desulfovibrio*) consistently increased in early stages of synucleinopathy. Most of these microbes were previously identified as RBD/PD-enriched bacteria. Among them, *Desulfovibrio* constitutes a group of hydrogen sulphide and lipopolysaccharide–producing bacteria. Lipopolysaccharide-treated mice developed intestinal hyperpermeability and greater accumulation of pathological alpha-synuclein. Notably, *Collinsella* is a hydrogen-reducing bacteria that can cross-feed with *Desulfovibrio*. *Collinsella* enrichment is associated with low-fibre diets and metabolic diseases; it may cause intestinal hyperpermeability by downregulating the expression of epithelial tight junctions.

Consistent with previous studies, constipation symptoms (ie, bowel movement frequency score) showed the strongest associations with gut microbiota features; 30% of the total effect of gut microbiota on prodromal PD passed through the mediator (bowel movement frequency score), indicating the potential direction of causality from gut dysbiosis to constipation to synucleinopathy.[3] This observation was supported by prior clinical trials in PD, whereby patients with PD who received pro-/prebiotics had significantly increased spontaneous bowel movement. Thus, drugs targeting constipation and specific microbes in early stages of disease might be important for future prevention and disease-modifying treatment of synucleinopathy.

Conclusions

Gut dysbiosis is likely present in early and prodromal stages of synucleinopathy. Gut microbiota might be a promising target for the early prevention and treatment of synucleinopathy.

Funding

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Disclosure

The results of this research have been previously published in:

1. Huang B, Chau SWH, Liu Y, et al. Gut microbiome dysbiosis across early Parkinson's disease, REM sleep behavior disorder and their first-degree relatives. Nat Commun 2023;14:2501.

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Ultra-early aneurysm treatment for patients with poor neurological status after intracranial aneurysm rupture: abridged secondary publication

GKC Wong *, COA Tsang, KY Yam, YC Po, KY Chan, KYV Pang, HKC Mak

KEY MESSAGES

1. Ultra-early aneurysm treatment is not associated with favourable modified Rankin Scale score at 6 months and is not a valid surrogate for outcomes.
2. The ultra-early and non-ultra-early aneurysm treatment groups are comparable at 1, 3, and 6 months in terms of Montreal Cognitive Assessment score, Stroke-Specific Quality of Life score, Short-Form 36 score, return to work status.

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Introduction

Intracranial aneurysm rupture resulting in aneurysmal subarachnoid haemorrhage (SAH) is a devastating form of cerebrovascular accident (CVA). In 2010, the overall incidence of SAH in Hong Kong was approximately 7.5 per 100 000 person-years. Most patients are unaware that they are at risk, despite reports of specific factors associated with SAH.

Although SAH only accounts for 5% of CVA cases, many of the affected patients are young (aged <65 years), leading to a loss of functional years comparable with that from ischaemic CVA. Worldwide, case fatality rates range from 8.3% to 66.7%. Recent studies suggest that SAH mortality has substantially declined over the past few decades. This improvement in SAH mortality reflects the use of more aggressive aneurysm treatment protocols and the implementation of modern critical care strategies. Thus, patients with SAH frequently require admission to intensive care units and high dependency units for close clinical monitoring and treatment. Ultra-early aneurysm treatment is defined as definitive aneurysm microsurgery, endovascular embolisation, or stenting to prevent rebleeding, all performed within 24 hours of ictus in aneurysmal SAH. In poor-grade aneurysmal SAH, ictus is defined as the time at which the patient developed reduced consciousness. Similarly, treatment beyond 24 hours is defined as definitive aneurysm microsurgery, endovascular embolisation, or stenting to prevent rebleeding, all performed >24 hours after ictus in aneurysmal SAH. Ultra-early aneurysm treatment for patients with SAH admitted with poor neurological status could serve as a surrogate for favourable functional outcomes at 6 months. We prospectively assessed patients with poor-grade SAH in Hong Kong to determine whether ultra-early treatment was a valid surrogate for clinical outcomes. Specifically, we evaluated whether ultra-early aneurysm treatment was associated with improved clinical outcomes in hospitalised patients with poor neurological status after intracranial aneurysm rupture.

Methods

This study was conducted between 1 August 2019 and 31 July 2022. Patients with aneurysmal SAH were recruited from seven hospitals in Hong Kong: Prince of Wales Hospital, Queen Mary Hospital, Princess Margaret Hospital, Kwong Wah Hospital, Tuen Mun Hospital, Queen Elizabeth Hospital, and Pamela Youde Nethersole Eastern Hospital. Ultra-early aneurysm treatment was defined as definitive cerebral aneurysm treatment (eg, coiling or clipping) within the first 24 hours after SAH. Non-ultra-early aneurysm treatment was defined as definitive cerebral aneurysm treatment >24 hours after SAH. Patients were followed up until 6 months post-SAH. Assessments were independently conducted at baseline, 30 days, 3 months, and 6 months by research assistants who were blinded to clinical management plans.

The primary outcome was modified Rankin

Scale (mRS) score at 6 months post-SAH. Secondary outcomes were Montreal Cognitive Assessment score, Stroke-Specific Quality of Life score, Short-Form 36 score, return to work status, and hospital resource utilisation at 30 days, 3 months, and 6 months. The mRS is validated for assessing recovery in patients with SAH. The mRS identifies activity limitations, which range from 0 (no symptoms) to 6 (death). Scores on the mRS were dichotomised as favourable (0-2) and unfavourable (3-6) for analysis. The Montreal Cognitive Assessment evaluates seven cognitive domains: visuospatial/executive function, naming, verbal memory registration and learning, attention, abstraction, 5-minute delayed verbal recall, and orientation. It is validated for assessing cognitive dysfunction and deficits in patients with SAH. The Stroke-Specific Quality of Life scale is validated for assessing disease-specific quality of life in patients with SAH. The Short-Form 36 is validated for assessing health-related quality of life in patients with SAH.

Sample size was calculated using Prince of Wales Hospital 2017 data, which showed that 49% of patients with SAH had ultra-early definitive aneurysm treatment. Post hoc analysis suggested that ultra-early aneurysm treatment increased the percentage of favourable outcomes at 6 months from 19% to 37%. With α=0.05 and β=0.2, the minimum sample size for each arm was 107. Logistic regression analyses were performed with adjustments for age, admission neurological grade, hypertension, and modality of aneurysm treatment. If quality of life outcomes showed improvement, incremental cost-effective ratios were calculated. A P value of <0.05 was considered statistically significant; all tests were two-tailed.

Results

Of the 659 patients with SAH screened, 235 had good-grade aneurysmal SAH, two had no SAH, 14 had traumatic SAH, and the remaining 408 had poor-grade aneurysmal SAH. Of the latter, 293 (72%) patients underwent ultra-early (n=163) or non-ultra-early (n=130) aneurysm treatment.

In univariable analysis, the proportion of patients with favourable mRS score (≤2) at 6 months was lower in the ultra-early treatment group (35% vs 22%, P=0.011). The significant difference remained after multivariable analysis (odds ratio=0.51, 95% confidence interval=0.28-0.93, P=0.027). Therefore, the results did not support our hypothesis that ultra-early aneurysm treatment would result in a higher proportion of patients with SAH to achieve mRS score ≤2 at 6 months. The ultra-early and non-ultra-early aneurysm treatment groups were comparable in terms of secondary outcomes at 1, 3, and 6 months. Because the quality of life outcomes did not suggest a benefit, we did not perform a cost-effectiveness analysis regarding hospital resource utilisation.

Discussion

Ultra-early aneurysm treatment was not a valid surrogate for outcomes in patients with poor-grade SAH. However, studies (mostly single-centre observational case series) have reported that ultra-early aneurysm treatment (especially endovascular treatment) for patients with poor-grade aneurysmal SAH is associated with better outcomes. Other management parameters (eg, blood pressure control) may play important roles.[1]

The median transfer time has been reported to be 4 days.[2,3] Patients with secondary events and deterioration are more likely to receive desperate measures during earlier aneurysm treatment, leading to poor outcomes. Five themes are identified as facilitators and barriers to timely treatment of aneurysmal SAH: 'early recognition' leads to urgent response; 'accessibility to health care' depends on patient's location, transport, and environmental conditions; good 'coordination' between and within health services is a key facilitator; 'complexity' of patient's condition affects time to treatment in multiple time periods; and 'availability of resources' is identified most frequently during the diagnostic and treatment phases as both barrier and facilitator.[4]

The present study has limitations. It is a pragmatic trial (without a unified experimental protocol for patient management), which is less robust than a randomised controlled clinical trial. Because of prior agreements that the results of various centres would not be analysed or disclosed, no subgroup analyses were performed. A total of 115 (28%) of patients did not consent to participate; reasons for lack of consent were not recorded for analysis.

Conclusions

Ultra-early aneurysm treatment is not associated with favourable mRS score at 6 months and is not a valid surrogate for outcomes.

Funding

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Cost-effectiveness of myopia control by use of defocus incorporated multiple segments lenses: abridged secondary publication

J Lian *, SM McGhee, MKH Yap, R Sum

KEY MESSAGES

1. Myopia control by use of defocus incorporated multiple segments lenses can prevent eye complications and severe visual impairment and is cost-effective from the societal perspective in terms of cost per quality-adjusted life year gained.
2. It is cost-effective for the government to subsidise myopia control and improve equity of access for defocus incorporated multiple segments lenses.

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Introduction

Myopia is the most common eye condition worldwide. Its prevalence is projected to increase from 23% to 50% of the global population between 2000 and 2050, and the global prevalence of high myopia is projected to increase from 2.7% to 9.8% over same period.[1] Hong Kong has an alarmingly high prevalence of myopia, particularly among school children: 18.3% of 6-year-olds are myopic, and the prevalence rises to almost 70% by age 17. High myopia can cause severe visual impairment due to ocular complications, including myopic macular degeneration, retinal detachment, glaucoma, and cataract. Many of these conditions cause irreversible vision loss. The socioeconomic impact of myopia is reflected in decreased quality of life and increased costs for individuals, public health care systems, and society related to care for ocular complications and visual loss.

Because the school years often exhibit the fastest myopia progression, this time period is crucial for myopia control. Various interventions have been developed to control myopia progression, including optical interventions (eg, spectacle lenses, soft contact lenses, and orthokeratology) and pharmacological interventions.[2-5] Orthokeratology has been routinely used for more than a decade in Hong Kong, and it reportedly reduces myopia progression by >40% if applied at the appropriate time.[4] Locally developed defocus incorporated multiple segments (DIMS) lenses constitute the latest spectacle design for myopia control. The efficacy of DIMS lenses in reducing myopia progression is 52%.[2] These lenses are easy to use and non-invasive and thus are potentially eligible for most people. Despite upfront costs, myopia control has potential benefits of avoiding vision loss related to high myopia-associated ocular complications, thereby improving quality of life.

The aim of this study was to evaluate the cost-effectiveness of myopia control through the use of DIMS lenses in children. We built a cost-effectiveness model to estimate the quality-adjusted life years (QALYs) gained and costs over a lifetime for myopia control, to conduct sensitivity and value of information analyses to quantify uncertainty in results and the value of reducing this uncertainty, and to examine cost-effectiveness from the perspectives of public health care, patients, and society.

Methods

A cost-effectiveness analysis was conducted to determine (1) whether myopia control is value for money from a societal perspective and (2) whether it is cost-effective for the government to subsidise myopia control to enable equitable access. We first compared the strategies of myopia control with 100% uptake versus no myopia control. This fairly reflects whether myopia control is value for money when financial barriers in uptake are absent and access is provided to all eligible children. We then compared the strategies of myopia control fully subsidised by the government with 80% uptake versus the current status quo, without subsidy, with 10% uptake.

An individual-based Markov state-transition model was developed based on the natural history of myopia development and progression. Individuals began with an initial level of myopia (none, mild, moderate, or high) and could progress to a higher level, develop myopia-related eye diseases, and eventually exhibit severe visual impairment (visual acuity <20/200). A cycle length of 1 year was used, and transitions between health states were simulated in each cycle over an individual's lifetime. Myopia

control interventions were incorporated into the natural disease progression to simulate how the receipt of myopia control in childhood affects progression to high myopia, thereby preventing sight-threatening eye diseases later in life. This model was developed using TreeAge Pro Suite 2020 (TreeAge Software, Inc, Williamstown, MA, USA).

The model simulated an individual's health states in childhood and adulthood. Phase 1 began with individuals randomly assigned to various ages (6 to 11 years), either sex, and various levels of myopia in terms of spherical equivalent refraction. Beginning in the first cycle, annual changes in spherical equivalent refraction were applied to individuals according to age, myopia level, and treatment status. For a myopic individual who received myopia control, smaller annual changes in spherical equivalent refraction were applied. The development and progression of myopia were simulated until age 18, when the myopia level became stable.

Phase 2 simulated the impact of myopia on the development of retinal detachment, myopic macular degeneration, cataract, and open-angle glaucoma. The annual transition probabilities of the diseases were applied at age 50. The development of each disease was simulated until the individual reached age 100 years, exhibited severe visual impairment, or died. Individuals with myopia, particularly high myopia, had higher probabilities of developing eye diseases. After the development of any eye disease, impact on vision was further simulated. The progression and decision pathways for each eye disease were simulated independently, and more than one disease could develop over an individual's lifetime.

In each cycle, utility decrement values were assigned based on the largest decrement among disease states that an individual could have. Individuals with severe visual impairment from any eye disease were not included in further simulations of other eye diseases, and the utility decrement for severe visual impairment was assigned to their remaining lifetime.

Lifetime costs and benefits were calculated and compared. Incremental cost-effectiveness ratios (ICERs) were calculated and compared with the willingness to pay (WTP) threshold for a QALY. All future costs and QALYs were first reported with no discount and then with a 3.5% discount rate on costs but no discount on QALYs (0%). We tested a 3.5% discount rate for QALYs in the scenario analysis. According to the World Health Organization (WHO)–recommended threshold, a 1-QALY gained is very cost-effective for up to 1 × annual gross domestic product (GDP) per capita (HK$377 165 in Hong Kong, 2019) and cost-effective for up to 2 × GDP. We conducted sensitivity analysis to determine how uncertainties regarding the parameters influenced cost-effectiveness.

Results

The cumulative prevalence of moderate myopia was 38.6% lower when using DIMS lenses than when not using myopia control (20.5% vs 33.3%), and the cumulative prevalence of high myopia was 47.9% lower (5.9% vs 11.3%), whereas the proportion of individuals who developed any complication of retinal detachment, myopic macular degeneration, or open-angle glaucoma was 14.3% lower (13.8% vs 16.1%), and the proportion with severe visual impairment was 17.5% lower (2.7% vs 3.3%).

With no discount on costs, use of DIMS lenses was cost-saving compared with no myopia control. Using a 3.5% discount rate on costs, the difference in incremental costs between DIMS lenses and no myopia control was HK$9913 (HK$57 850 vs HK$47 937) and difference in incremental QALYs gained was 0.19 (72.78 vs 72.59); thus, the ICER of myopia control was HK$52 792 per QALY gained. Using a 3.5% discount rate on QALYs, the ICER of myopia control was HK$181 794 per QALY gained. In probabilistic sensitivity analysis, myopia control using DIMS lenses had >50% probability of being cost-effective when the WTP for a QALY was ≥HK$35 000; the probability of being cost-effective was 79% when the WTP reached the WHO-recommended threshold of HK$377 165. One-way sensitivity analysis showed that the five parameters with the greatest impact on the ICER were utility decrements on mild, moderate, and high levels of myopia, cost of DIMS lenses, and effectiveness of DIMS lenses. However, all ICERs (up to HK$146 120) across the test range of these parameters' values were within the WHO-recommended threshold.

From a government perspective, when only costs were discounted at 3.5%, the difference in incremental cost between myopia control with subsidy and myopia control with no subsidy was HK$8701 (HK$11 905 vs HK$3204), and the incremental QALYs gained was 0.15 (72.77 vs 72.61). Thus, the ICER was HK$56 797 per QALY gained. Probabilistic sensitivity analysis showed that myopia control with subsidy had >50% probability of being cost-effective when the WTP for a QALY was ≥HK$43 000; the probability of being cost-effective was 72% when the WTP reached the WHO-recommended threshold of HK$377 165. When QALYs gained were discounted at 3.5%, the ICER was HK$209 000 per QALY gained.

Discussion

The model demonstrated that myopia control by use of DIMS lenses can potentially reduce the development of any complications of retinal detachment, myopic macular degeneration, and/or

open-angle glaucoma) by 14.3% and the development of severe vision impairment (visual acuity worse than 20/200) by 17.5% over a lifetime. The cost per individual spent on DIMS lenses was HK$9913 more after subtracting future savings gained (through avoiding more expensive spectacles for severe myopia, greater health care utilisation, increased patient time spent in treatment and follow-up for eye complications, and productivity loss secondary to severe vision impairment). Using the WHO-recommended threshold of HK$377 165 per QALY, use of DIMS lenses was cost-effective with an ICER of HK$52 792 per QALY gained. When the discount rate for QALYs was 3.5%, the ICER increased (HK$181 794) but remained below the WHO-recommended threshold for cost-effectiveness. From a government perspective, subsidising DIMS lenses was cost-effective with ICERs below the WHO-recommended threshold.

Conclusion

Myopia control by use of DIMS lenses is potentially cost-effective for society. A government-subsidised programme could be a cost-effective option to improve equity of access.

Funding

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Cost-effectiveness of prophylaxis with palivizumab among high-risk children in Hong Kong: abridged secondary publication

P Wu *, BJ Cowling, SS Chiu, IOL Wong, WKY Yeung

KEY MESSAGES

1. Prophylaxis with palivizumab administered after start of respiratory syncytial virus seasons identified by moving epidemic method (ie, one-peak seasons typically starting in April and ending in October or later) was the most cost-effective strategy when used for infants with congenital heart disease and Down syndrome or extreme preterm delivery with bronchopulmonary dysplasia.
2. Our findings can provide insights into further investigations concerning long-lasting monoclonal antibodies and vaccines.

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Introduction

Respiratory syncytial virus (RSV) causes acute respiratory tract infections in humans every year, including bronchiolitis and pneumonia in children aged <5 years and insidious respiratory illness in older adults. Prophylactic therapy with the monoclonal antibody, palivizumab, has been recommended by the American Academy of Pediatrics (AAP) to reduce occurrences of severe RSV infection in high-risk infants. However, there has been a lack of consensus concerning the target population and treatment schedule, given the high treatment cost and regional variations in RSV seasonality.[1] We conducted this study to systematically evaluate the cost-effectiveness of palivizumab in reducing the burden of RSV-associated disease in Hong Kong, considering the seasonal patterns and health impact of RSV in the local population.

Methods

Data for age-specific weekly hospitalisation between 1998 and 2015 in Hong Kong were obtained from the Hospital Authority. Data for weekly rates of respiratory virus detection in sentinel surveillance samples were provided by the Centre for Health Protection, as were data for weekly rates of influenza-like illness consultations at sentinel outpatient clinics. Data for hospitalised infants with laboratory-confirmed RSV infection between 2004 and 2011 were collected from two public hospitals (Queen Mary Hospital and Pamela Youde Nethersole Eastern Hospital), including dates of birth, admission and discharge, gestational age at birth, high-risk conditions, and test results of RSV infection, as well as infants with potentially high RSV infection risk but no laboratory-confirmed RSV infection during hospitalisation. Seven high-risk groups were investigated based on recommendations from the AAP[2]: (1) extreme preterm delivery (born at ≤28 weeks gestational age) with or without (2) bronchopulmonary dysplasia and with (3) chronic lung disease or bronchopulmonary dysplasia, (4) haemodynamically significant congenital heart disease, (5) Down syndrome, (6) neuromuscular impairment, and (7) congenital heart disease and Down syndrome.

Results

We first examined the population-level impact of RSV infection on respiratory hospitalisation in Hong Kong among infants aged <1 year, children aged 1-5 years, and older adults aged ≥65 years. Then, we characterised RSV seasonality by three approaches: (1) time series analysis of the standardised weekly ratio of RSV-associated hospitalisation estimated as the weekly RSV-associated excess respiratory hospitalisation rate among infants divided by the maximum weekly excess respiratory hospitalisation rate in the same year according to regression models, (2) a moving epidemic method, and (3) a threshold method that analysed RSV virus activity based on sentinel surveillance. The results showed that Hong Kong, a subtropical city, had a prolonged RSV season in most years, without regular epidemic peaks. RSV activity generally started between February and March every year and remained relatively high for 6 months during which >80% of RSV-associated respiratory hospitalisations occurred.

Based on the RSV seasonality in Hong Kong, the cost-effectiveness of palivizumab use in the high-risk groups was estimated by decision tree analysis. The incremental cost-effectiveness ratio (ICER) was measured as the change in cost per hospital admission prevented (HAP) under the following four strategies: (1) prophylaxis administered in the weeks with the highest RSV-attributable burden of hospitalisation (weeks 12 to 18, and 27 to 38); (2) prophylaxis administered after start of RSV seasons identified by moving epidemic method (ie, one-peak seasons typically starting in April and ending in October or later); (3) prophylaxis administered after start of RSV seasons determined by the threshold method (ie, one-peak annual seasons between weeks 5-10 and 40-45, based on a threshold of the 30th percentile of weekly RSV activity in that year); (4) prophylaxis administered throughout the year (weeks 1 to 52), whereby each high-risk infant received an injection of palivizumab once per month.

Strategy 2 was superior because it showed the lowest estimated ICERs to prevent one RSV-associated hospital admission. Strategy 1 showed slightly higher estimated ICERs for different risk groups. Strategy 2 was generally more cost-effective when used for infants with congenital heart disease and Down syndrome (US$42 000 per HAP) or extreme preterm delivery with bronchopulmonary dysplasia (US$50 900 per HAP). It was less cost-effective when recommended for widespread use among infants with haemodynamically significant congenital heart disease, chronic lung disease or bronchopulmonary dysplasia, and extreme preterm delivery with bronchopulmonary dysplasia, because efficacy of palivizumab was lower in these patients. Strategy 2 was moderately cost-effective (US$91 400 per HAP) among infants with neuromuscular impairment, which is rare in Hong Kong. Extreme preterm infants without bronchopulmonary dysplasia had the highest ICER estimate.

Discussion

The considerable respiratory hospitalisation burden was potentially attributable to RSV infection, particularly in children aged <5 years, considering the prolonged RSV season in Hong Kong. Widespread use of palivizumab among infants with high-risk conditions as recommended by the AAP may not be appropriate in Hong Kong, given the variable RSV seasonality and the characteristics of high-risk infants in Hong Kong. At the end of this study, palivizumab was the only available medication for RSV prophylaxis. Since 2022, Beyfortus (nirsevimab)[3] for neonates and infants, and Arexvy (RSV vaccine) from GSK[4] and Abrysvo (RSV vaccine) from Pfizer[5] for older adults, have been approved for use to prevent severe RSV infection. Our findings can provide insights into further investigations concerning long-lasting monoclonal antibodies and vaccines.

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Influenza ADCC-antibody responses in vaccinated and infected children as a correlate of protection: abridged secondary publication

S Valkenburg *, BJ Cowling, NHL Leung

KEY MESSAGES

1. Pandemic haemagglutinin IgG responses are boosted by recent seasonal vaccination and decline within 1 year and reach baseline by 5 years post-vaccination.
2. Correlation is strong between FcR binding and antibody-dependent cellular cytotoxicity function, validating the use of multiplex bead approaches to quantify antibody responses.
3. Vaccination increased IgG1 responses to vaccine and pandemic proteins (HA H3 H1, neuraminidase, nucleoprotein).
4. Unvaccinated uninfected children had increased H1/09 IgG and FcγRIIIA, compared with unvaccinated children who became infected. This indicates that higher baseline pandemic-specific antibodies coincide with protection.
5. Antibody diversity is increased by vaccination and infection, but the diversity does not extend to avian influenza viruses.

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Introduction

Influenza viruses are extremely diverse, and vaccine-mediated protection by available whole-virion inactivated vaccines elicits strain-specific neutralising antibodies as its main protective function. Vaccine efficacy is dependent on haemagglutinin (HA) matching; it varies from 0% to 80% depending on the year and age group. In 2009, seasonal influenza vaccination in children resulted in 47% vaccine effectiveness against H1N1pdm influenza virus.[1] Yet, some classes of antibodies can cross-react among seasonal, pandemic, and avian influenza viruses. These antibodies may play a protective role in limiting the acquisition or severity of influenza virus infection. We aimed to determine whether the magnitudes of antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis responses are enhanced by vaccination and reduce the risk of influenza virus infection with stable responses.

Methods

We utilised a large biobank of immune serum from a randomised control trial of vaccination in children (NCT00792051), whereby children were vaccinated in 2008 with trivalent seasonal influenza vaccines containing H1N1 A/Brisbane/2007 virus or placebo, prior to the H1N1 A/California/2009 pandemic. The cohort was followed over the subsequent 5 years (2009 to 2014) to assess rates of reverse transcription–polymerase chain reaction-confirmed infection.

To quantify influenza-specific antibodies before and after vaccination, and before and after pandemic infection, we used a systems serology approach involving ADCC natural killer (NK) cell-based assays, as well as a multiplex bead approach that couples FcR dimer proteins,[2] diverse HA proteins including HA-stem constructs, and antibody subclasses (IgG1/2/3) and isotypes (IgG/A1). The multiplex bead approach was validated with a flow-cytometric NK cell-based assay[3] to identify influenza-specific ADCC-antibody activities with strong correlations.

Results

Vaccination increased HA-specific antibodies in terms of magnitude and FcR effector functions including antibodies to the pandemic virus H1/2009 HA and neuraminidase proteins. These antibody levels declined within 1 year post-vaccination and then remained stable, similar to other viral proteins. Total H1/2009 HA IgG and IgG2 levels were higher in vaccinated uninfected children than in unvaccinated infected children. This suggests a protective role for cross-reactive HA antibodies. However, although vaccination increased IgG1 responses to the vaccine and related proteins, it did not affect infection status and possibly masked baseline protective effects in unvaccinated uninfected children. There

was strong correlation between FcR binding and ADCC function, validating the use of multiplex bead approaches to quantify antibody responses (data not shown).

We compared the diversities of HA antibody responses to seasonal, pandemic, and avian HA proteins. We also compared total antibody responses to determine the effects of vaccination and infection on cross-reactivity. Antibody effector responses were boosted by vaccination, but vaccine-breakthrough infections occurred despite these increased responses. Therefore, other immune parameters may contribute to virus protection.

Discussion

Seasonal vaccination increased IgG responses to a non-vaccine component (the HA-H1/2009 protein) and resulted in vaccine-mediated protection in 47% of children during the early H1N1 pandemic.[1] Therefore, seasonal vaccination should be encouraged for pandemic viruses where cross-reactivity may provide some residual protection. Baseline elevated HA-H1/2009-specific IgG and FcγRIIIA levels in unvaccinated children coincided with protection from infection, and the sources of elevated baseline protective responses and vaccines that can stimulate these responses should be investigated.

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Community burden of hepatitis A infection and risk of transmission in Hong Kong

NS Wong, DPC Chan, CP Chan, CM Poon, SS Lee *

KEY MESSAGES

1. The age/sex-adjusted prevalence of anti-hepatitis A virus antibodies was 39.25% among 2085 participants in a population survey in Hong Kong.
2. The estimated age at midpoint of population immunity for hepatitis A infection was 45 to 49 years, more than 30 years older than that estimated half a century ago.
3. Only 3% of participants gave a definitive history of previous hepatitis A vaccination.
4. Hepatitis A vaccine uptake was associated with employment in higher-risk occupations and frequent travel.
5. A household survey using building groups as sampling frame was a practical approach for developing epidemiologic analyses.

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Introduction

Hepatitis A virus (HAV) is transmitted through the oral-faecal route. Because of improvements in sanitation and access to clean water worldwide, the incidence of hepatitis A has fallen. However, the age-standardised incidence rates remain static, as revealed in the Global Burden of Disease Study in 2019.[1] Despite epidemiological improvements, there is a paradox: incidents of HAV foodborne outbreaks are increasing in high-income countries, whereas the transition from high to low endemicity in middle- and low-income countries is leading to increases in symptomatic diseases.[2] HAV vaccines, licensed in the 1990s, are highly immunogenic and can elicit long-lasting immunity. The susceptibility of a population to HAV infection depends on the interplay between the extent of natural infection and the effects of HAV vaccination. Vaccination coverage varies according to sociodemographic profile, local endemicity, and vaccination strategies.

In 2001, approximately 71% of Hong Kong adults in a population survey had detectable anti-HAV antibodies, largely because of natural infection.[3] Between 2001 and 2020, the yearly number of HAV cases reported to the Department of Health has steadily declined. In 2020, there were 28 reported HAV cases. In the past decade, there was a clear increase in the proportion of reported cases among people aged ≥45 years. However, major outbreaks have not occurred since the 1990s, despite the lack of public HAV vaccination programmes. Therefore, we conducted a seroprevalence study to evaluate the population risk of HAV and the role of vaccination in preventing HAV transmission in Hong Kong.

Methods

This study formed part of a prospective cross-sectional hepatitis A and B household survey, and the full protocol of which has been published.[4] Eligible members of spatially randomised households were invited to complete a questionnaire and provide blood samples for serological testing. The questionnaire covered demographics, medical history of hepatitis infection, exposure risk, and vaccination history. Serological analyses of anti-HAV IgG antibodies were performed by immunoassay.

The crude and age/sex-adjusted prevalences of anti-HAV antibodies were measured. The age at midpoint of population immunity (AMPI) was estimated,[5] which was defined as the youngest age at which ≥50% of the population had serologic evidence of prior HAV infection. A bivariable logistic regression model was used to compare participants who self-reported definitively or likely to have received the HAV vaccine with participants who self-reported definitively not or unlikely to have received the HAV vaccine. Multivariable logistic regression was conducted with age at survey year as a confounder. Complete case analyses were performed.

Results

Between September 2018 and October 2020, we sent 38 020 invitation letters by post, and respondents

TABLE 1. Characteristics of participants (n=2085)

Characteristic	Value*
Sex	
Female	1175 (56.4)
Male	910 (43.6)
Age, y (n=2085)	54 (39-63)
Ethnicity (n=2073)	
Non-Chinese	13 (0.6)
Chinese	2060 (99.4)
Permanent resident of Hong Kong (n=2072)	
No	41 (2.0)
Yes	2031 (98.0)
Born in Hong Kong (n=2084)	
No	598 (28.7)
Yes	1486 (71.3)
Marital status (n=1999)	
Never married	500 (25.0)
Widowed	104 (5.2)
Separated	7 (0.4)
Divorced	148 (7.4)
Married	1240 (62.0)
Education level (n=2078)	
Secondary and below	1192 (57.4)
Post-secondary	886 (42.6)
Currently employed (n=1997)	
No	844 (42.3)
Yes	1153 (57.7)
History of hepatitis or other liver disease	
Liver disease (n=2080)	
No	1948 (93.7)
Yes	132 (6.3)
Fatty liver	
No	1965 (94.2)
Yes	120 (5.8)
Cirrhosis	
No	2082 (99.9)
Yes	3 (0.1)
Liver cancer	
No	2081 (99.8)
Yes	4 (0.2)

* Data are presented as No. (%) of participants or median (interquartile range)

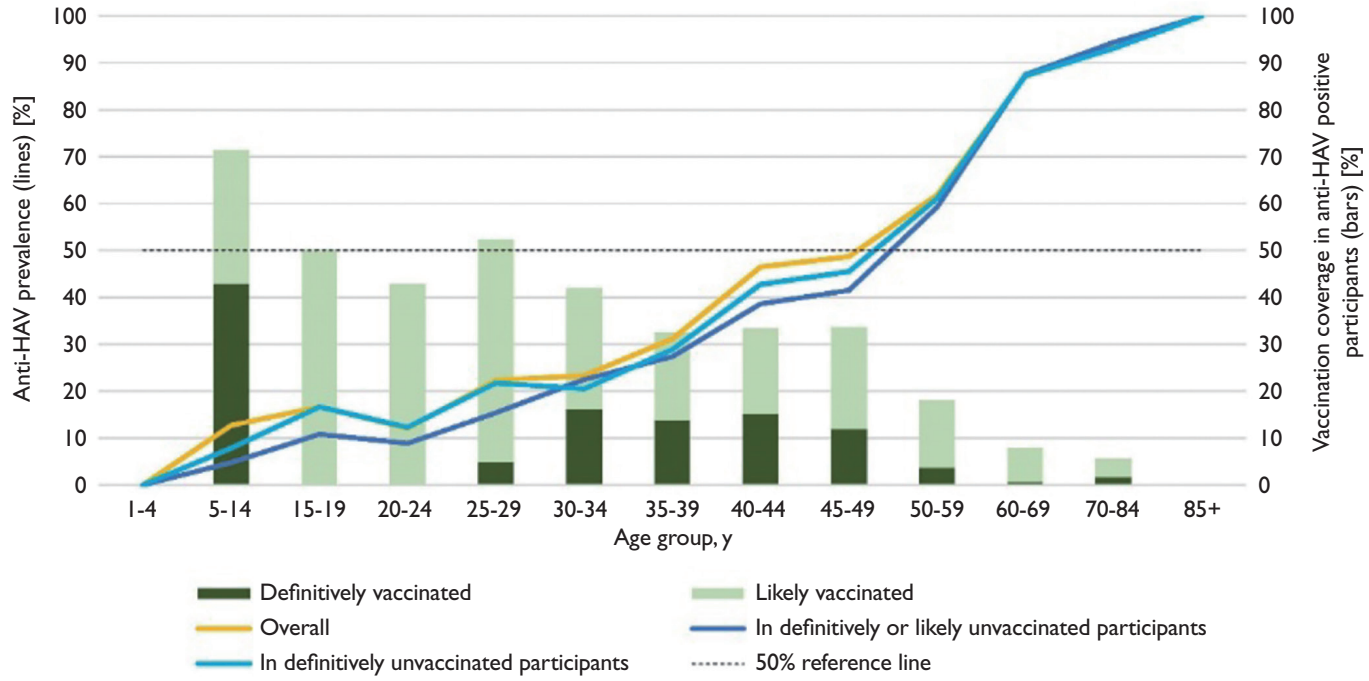

FIG. Hepatitis A virus (HAV) vaccination history and anti-HAV antibody prevalence in study population according to age

from 1497 (4%) households agreed to participate. Among 2085 participants, the median age was 54 years and the male-to-female ratio was 0.77; 99% of participants were Chinese and 71% of the participants were born in Hong Kong (Table 1). Compared with 2016 census, our participants had higher proportions of Chinese ethnicity, female, age ≥35 years, and post-secondary education. The distribution of recruited households among districts was within 2% of the distribution in residential building groups.

The crude prevalence of anti-HAV antibodies was 58.87% (1218/2069, 95% confidence interval [CI]=56.75%-60.99%), which became 39.25% (95% CI=37.14%-41.35%) after adjustments for age and sex. The anti-HAV antibody prevalence was positively associated with age (Fig). Approximately 89% of respondents aged ≥60 years were anti-HAV antibody-positive, compared with 14% of respondents aged <25 years. The estimated AMPI was 45-49 years.

Only 64 (3%) of participants gave a definitive history of HAV vaccination. Among anti-HAV antibody-positive participants, the percentage of participants with a definitive history of vaccination was highest among people aged 5 to 14 years (43%), followed by people aged 30 to 49 years (16%) [Fig]. Vaccination history (definitive or likely) was associated with younger age (odds ratio [OR]=0.97, 95% CI=0.96-0.98), higher education level (adjusted OR [aOR]=2.40, 95% CI=1.87-3.07), and being employed (aOR=1.69, 95% CI=1.29-2.23). People working in higher-risk occupations (eg, laboratory workers, sewage workers, food handlers, zookeepers, veterinarians, and researchers in contact with non-human primates) were more likely to have received the HAV vaccine (aOR=2.05, 95% CI=1.23-3.39). Frequent travellers who had more than one trip per year were more likely to be vaccinated, compared with travellers who had one trip every year (aOR=0.67, 95% CI=0.51-0.89) and travellers who had one trip every 2 to 3 years (aOR=0.52, 95% CI=0.36-0.77). A history of travel to HAV-endemic areas (aOR=1.34, 95% CI=1.03-1.74) or Southeast Asia (aOR=1.64, 95% CI=1.17-2.28) was also associated with vaccine uptake (Table 2).

Discussion

Considering its age/sex-adjusted anti-HAV antibody prevalence of <40%, Hong Kong is transitioning from high to low endemicity. We estimated AMPI, an index of HAV endemicity,[2] to assess epidemiologic burden. High-income countries with low endemicity typically have an AMPI of ≥50 years, in contrast to the AMPI of <5 years in low-income countries with high endemicity. In Hong Kong, the estimated AMPI was 11 to 20 years in the late 1970s, 21 to 30 years in the late 1980s, and 30 to 39 years in 2001,[3] compared

TABLE 2. Factors associated with self-reported hepatitis A virus vaccination (n=2081)

	Self-reported hepatitis A vaccination history		Odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
	No (n=1731)*	Yes (n=350)*		
Sex				
Female	981 (56.7)	192 (54.9)	Reference	Reference
Male	750 (43.3)	158 (45.1)	1.08 (0.85-1.36)	1.06 (0.83-1.34)
Age, y	56 (42-64)	44 (31-55)	0.97 (0.96-0.98)†	-
Age group, y				
<20	87 (5.0)	24 (6.9)	2.37 (1.46-3.86)†	-
20-29	113 (6.5)	44 (12.6)	3.35 (2.26-4.96)†	
30-39	187 (10.8)	85 (24.3)	3.91 (2.85-5.36)†	
40-49	261 (15.1)	71 (20.3)	2.34 (1.70-3.22)†	
≥50	1083 (62.6)	126 (36.0)	Reference	
Ethnicity (n=2069)				
Non-Chinese	9 (0.5)	4 (1.2)	Reference	Reference
Chinese	1713 (99.5)	343 (98.8)	0.45 (0.14-1.47)	0.51 (0.15-1.74)
Permanent resident of Hong Kong (n=2068)				
No	34 (2.0)	7 (2.0)	Reference	Reference
Yes	1687 (98.0)	340 (98.0)	0.98 (0.43-2.23)	1.37 (0.59-3.17)
Born in Hong Kong (n=2080)				
No	515 (29.8)	83 (23.8)	Reference	Reference
Yes	1216 (70.2)	266 (76.2)	1.36 (1.04-1.77)†	1.12 (0.85-1.48)
Ever married (n=1997)				
No	388 (23.3)	112 (33.8)	Reference	Reference
Yes	1278 (76.7)	219 (66.2)	0.59 (0.46-0.77)†	1.36 (0.99-1.87)
Education level (n=2074)				
Secondary and below	1065 (61.8)	124 (35.4)	Reference	Reference
Post-secondary	659 (38.2)	226 (64.6)	2.95 (2.32-3.74)†	2.40 (1.87-3.07)†
Currently employed (n=1995)				
No	755 (45.4)	88 (26.4)	Reference	Reference
Yes	907 (54.6)	245 (73.6)	2.32 (1.78-3.01)†	1.69 (1.29-2.23)†
Healthcare worker (n=1987)				
No	1577 (95.2)	311 (94.2)	Reference	Reference
Yes	80 (4.8)	19 (5.8)	1.20 (0.72-2.02)	1.10 (0.65-1.87)
Higher-risk occupations (n=1989)			Reference	Reference
No	1596 (96.4)	309 (92.8)	2.07 (1.27-3.37)†	2.05 (1.23-3.39)†
Yes	60 (3.6)	24 (7.2)		
Anti-hepatitis A virus antibody result (n=2065)				
Negative	704 (41.0)	144 (41.5)	Reference	Reference
Positive	1014 (59.0)	203 (58.5)	0.98 (0.77-1.24)	2.22 (1.66-2.97)†
Any liver disease (n=2077)				
No	1614 (93.5)	331 (94.6)	Reference	Reference
Yes	113 (6.5)	19 (5.4)	0.82 (0.50-1.35)	1.07 (0.64-1.77)

* Data are presented as No. (%) of participants or median (interquartile range)
† P<0.05

TABLE 2. (cont'd)

	Self-reported hepatitis A vaccination history		Odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
	No (n=1731)*	Yes (n=350)*		
Self-reported history of hepatitis A diagnosis (n=2078)				
No	1680 (97.2)	343 (98.0)	Reference	Reference
Yes	48 (2.8)	7 (2.0)	0.71 (0.32-1.59)	0.98 (0.44-2.21)
Travel to high endemic areas (n=2058)				
Never	1254 (73.3)	246 (70.9)	Reference	Reference
Ever	457 (26.7)	101 (29.1)	1.13 (0.87-1.45)	1.34 (1.03-1.74)†
Travel to Mainland China, Macau SAR, and/or Taiwan (n=2076)				
Never	5 (0.3)	2 (0.6)	Reference	Reference
Ever	1722 (99.7)	347 (99.4)	0.50 (0.10-2.61)	0.46 (0.08-2.57)
Travel to Southeast Asia (n=2076)				
Never	328 (19.0)	50 (14.3)	Reference	Reference
Ever	1399 (81.0)	299 (85.7)	1.40 (1.02-1.94)†	1.64 (1.17-2.28)†
Travel frequency in the past 10 years (n=2076)				
None	46 (2.7)	3 (0.9)	0.25 (0.08-0.82)†	0.36 (0.11-1.19)
Every >3 years	188 (10.9)	29 (8.3)	0.60 (0.39-0.92)†	0.67 (0.43-1.03)
Every 2-3 years	283 (16.4)	39 (11.2)	0.54 (0.37-0.78)†	0.52 (0.36-0.77)†
Every year	526 (30.5)	102 (29.2)	0.75 (0.58-0.99)†	0.67 (0.51-0.89)†
<1 year	684 (39.6)	176 (50.4)	Reference	Reference

with 45 to 49 years in the current study. The AMPI has increased by about 10 years per decade. Because of the increasing AMPI, young and middle-aged adults now have a higher risk of symptomatic HAV diseases, compared with half a century ago.

In Hong Kong, our study estimated that only 3% of the population have HAV vaccination. Natural infection continues to be the main factor for population immunity development. Although the anti-HAV antibody prevalence in unvaccinated people increased with age, the susceptibility to infection (indicated by the percentage of anti-HAV antibody-negative people) decreased with age. The low vaccination coverage (especially in young people) and the decrease in HAV disease incidence may lead to episodic outbreaks. In 2017, an unusual increase in HAV infection among men who have sex with men (MSM) occurred because of oral-anal sex in an unvaccinated young population. Worldwide, transmission clusters have occasionally occurred after consumption of contaminated produce and seafood imported from endemic countries. This highlights the effects of globalisation and international food trade.[2]

Participants with a higher risk of HAV transmission were more likely to have received the HAV vaccine. However, the overall rate of vaccination remained low. In the United States, routine vaccination is recommended for children aged 12 to 23 months and catch-up vaccination for children aged 2 to 18 years who have not previously vaccinated, as well as vaccination for adults with a risk of HAV infection or severe disease. In the absence of a universal vaccination programme, targeted strategies for increasing HAV vaccination coverage in selected vulnerable populations are needed to minimise the risk of outbreaks and the community burden of symptomatic disease.

The present study had limitations. First, the response rate was low (around 4%), and the recruitment was slowed by the COVID-19 pandemic. Second, there may have been self-selection bias because some individuals might have already known their infection status. Third, self-reported vaccination history could not be validated; some participants might have confused hepatitis B virus and HAV. Nevertheless, this study showed that the use of socially homogenous groups is robust for population survey for epidemiological analyses in Hong Kong.

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AUTHOR INDEX

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