SUPPLEMENT 6

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Research Dissemination Reports

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研究成果報告

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Supplement 6

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HONG KONG MEDICAL JOURNAL 香港醫學雜誌
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Health and Health Services Research Fund

Research Dissemination Reports

PAEDIATRICS

Editorial

Dissemination reports are concise informative reports of health-related research supported by funds administered by the Food and Health Bureau, for example the *Health and Health Services Research Fund* (which was consolidated into the *Health and Medical Research Fund* in December 2011). In this edition, ten dissemination reports of projects related to health economics, cardiovascular diseases, mental health, and paediatrics are presented. In particular, three projects are highlighted due to their potentially significant findings, impact on healthcare delivery and practice, and/or contribution to health policy formulation in Hong Kong.

Screening to detect early colorectal neoplasms can significantly reduce the incidence and mortality of colorectal cancers, but there is no agreed policy on colorectal cancer screening for Chinese populations in Hong Kong. Lam et al.[1] evaluated, inter alia, the health-related quality of life (HRQOL) of patients with different stages of colorectal neoplasms and the cost-effectiveness of colorectal cancer screening strategies from the healthcare service provider perspective in Hong Kong. They found that Chinese patients with colorectal neoplasms reported worse physical HRQOL but better mental HRQOL compared to the Hong Kong general population. In terms of screening options, immunochemical faecal occult blood testing every 2 years was the most cost-effective colorectal cancer screening strategy at an incremental cost-effectiveness ratio of HK$43 660 per quality-adjusted life-year gain.

Perioperative myocardial ischaemia is a common complication after non-cardiac surgery and is associated with serious morbidity and mortality. Endothelial dysfunction may play an important role in perioperative myocardial injury, and its rapid assessment could represent a novel method for cardiac risk stratification prior to surgery. Chan and Gin[2] evaluated the performance of preoperative endothelial function testing to predict perioperative ischaemia and 30-day cardiac complications in 600 intermediate-to-high risk patients undergoing non-cardiac surgery. Non-invasive assessment of endothelial function provided additional predictive value, beyond clinical variables, for preoperative risk stratification of postoperative myocardial ischaemia and major cardiac complications.

In people with severe mental illness, health needs assessment is essential in identifying unmet health needs and psychosocial influences that may impact their health. Mak et al.[3] conducted the first systematic examination of the health needs and lifestyle practices of 600 people with severe mental illness in Hong Kong, and determined how the psychosocial determinants of these health issues and practices relate to quality of life. In general, people with severe mental illness had poor health profiles and lower quality of life compared to the general population with moderate levels of unmet needs. To promote overall recovery and maximise the quality of life of people with severe mental illness, service providers should increase awareness of people with severe mental illness about their health needs and encourage practice of more health-promoting behaviour and preventive health care.

A research impact evaluation was conducted 2 years after the project end date for all of the studies reported in this supplement. Impact was reported through knowledge generation, capacity building, and influence on health policy and health care practices through changes in behaviour of health care professionals and/or other decision makers.

We hope you will enjoy this selection of research dissemination reports. Electronic copies of these dissemination reports and the corresponding full reports can be downloaded individually from the Research Fund Secretariat website (http://www.fhb.gov.hk/grants). Researchers interested in the funds administered by the Food and Health Bureau also may visit the website for detailed information about application procedures.

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Health-related quality of life in patients with colorectal neoplasm and cost-effectiveness of colorectal cancer screening in Hong Kong

CLK Lam *, WL Law, JTC Poon, P Chan, CKH Wong, SM McGhee, DYT Fong

KEY MESSAGES

1. Compared with the Hong Kong general population norm, Chinese patients with colorectal neoplasm (CRN) reported worse physical health-related quality of life (HRQOL) but better mental HRQOL and comparable health preference scores.
2. The CRN stage at diagnosis was the most significant determinant of HRQOL. Colorectal cancer was associated with worse physical HRQOL and health preference scores.
3. Immunochemical faecal occult blood testing every 2 years is the most cost-effective colorectal cancer screening strategy, with an incremental cost-effectiveness ratio of HK$43 660 per quality-adjusted life year gained.

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Introduction

The prevalence of colorectal neoplasms (CRN), including both cancer and pre-cancerous polyps, has been estimated to be 21% in Hong Kong Chinese aged >50 years.[1] Screening to detect early-stage CRN can reduce the incidence and mortality of colorectal cancers (CRC), but the cost-effectiveness of CRC screening in terms of quality-adjusted life years (QALYs) has never been evaluated in a Chinese population. This study aimed to determine the health-related quality of life (HRQOL) and health preference (utility) of patients with different stages of CRN and to evaluate the cost-effectiveness of CRC screening from the health care provider perspective in Hong Kong.

Methods

Between October 2009 and July 2010, 566 Chinese adult patients who were diagnosed with different stages of CRN for >6 months were recruited from the Queen Mary Hospital. The six stages of CRN were: (1) low-risk polyps (≤2 adenomas or 3-4 adenomas, all <1 cm), (2) high-risk polyps (≥5 adenomas or ≥3 adenomas, at least one >1 cm), (3) stage I CRC, (4) stage II CRC, (5) stage III CRC, and (6) stage IV CRC. Patients were excluded if they had <6 months of life expectancy, were unable to communicate in Cantonese or too ill to carry out an interview, or had known cognitive impairment.

A total of 553 (97.7%) patients completed an assessment by trained interviewers through telephone or face-to-face interview using a questionnaire that consisted of version 4 of the traditional Chinese (Hong Kong) Functional Assessment of Cancer Therapy-Colorectal Cancer (FACT-C), version 2 of the Chinese (Hong Kong) SF-12 Health Survey (SF-12v2), the Chinese version of the SF-6D Health Survey, and questions on socio-demographic and clinical characteristics.

The HRQOL scores of the six CRN stages were compared using the one-way ANOVA with Tukey's post hoc test. The HRQOL scores between CRN patients and the general population,[2] and among different CRN groups were compared. The FACT-C total, health preference, and physical and mental component scores (PCS and MCS) of SF-12v2 were used as dependent variables in the regression analysis. Multivariate linear regression analysis was used to determine the effect of clinical factors on dependent variables, controlling for the effects of socio-demographic factors. The R^2 and adjusted R^2 representing the total variances of dependent variables explained were reported together with the corresponding regression analyses. A P value of <0.05 was considered statistically significant.

Using the Markov Model, a hypothetical static cohort of 100 000 Hong Kong people aged 50 years and their health histories were simulated by gender groups until 75 years old. The natural history of

CRN was reflected in the model via the transitions between different health states and mortalities. The health states of CRN were divided into four sections: (1) the pre-CRC section (normal colonic epithelium, low-risk polyps, and high-risk polyps), (2) the undiagnosed CRC section (undiagnosed stage I, stage II, stage III, and stage IV CRC), (3) the diagnosed CRC section (diagnosed stage I, stage II, stage III, and stage IV CRC), and (4) the death section (death from CRC, death from screening complications, and death from other causes). All health states were modelled as Markov states with a 1-year cycle. All health states were at risk of progression to a more advanced stage or death, but were prohibited from returning to former health states, except for patients with low-risk or high-risk polyps who could return to normal colonic epithelium following polypectomy. Undiagnosed CRC was at risk of progression to a more advanced stage of CRN and mortality from CRC or other causes. Each year, patients with undiagnosed CRN had a specific probability of being diagnosed that may be altered by screening. It was assumed that the risk of disease progression was eliminated once CRC was diagnosed and treated, but the risk of mortality from CRC or other causes remained.

Thirteen screening strategies were compared using a decision analytic model based on a state-transition Markov process. The strategies were: (1) no screening (control), (2) annual guaiac faecal occult blood test (G-FOBT) [G-FOBT1], (3) annual human haemoglobin immunochemical-based FOBT (I-FOBT) [I-FOBT1], (4) biennial G-FOBT (G-FOBT2), (5) biennial I-FOBT (I-FOBT2), (6) sigmoidoscopy every 5 years (SIG5), (7) sigmoidoscopy every 10 years (SIG10), (8) colonoscopy every 5 years (COL5), (9) colonoscopy every 10 years (COL10), (10) annual G-FOBT plus sigmoidoscopy every 5 years (G-FOBT1+SIG5), (11) annual G-FOBT plus sigmoidoscopy every 10 years (G-FOBT1+SIG10),

TABLE 1. Baseline health-related quality of life and SF-6D preference scores by colorectal neoplasm stages

Scale*	Hong Kong norm	Total (n=515)	Colorectal neoplasm stage						Multiple comparison†
			(1) Low risk (n=85)	(2) High risk (n=66)	(3) Stage I (n=80)	(4) Stage II (n=99)	(5) Stage III (n=109)	(6) Stage IV (n=76)	
Mean±SD Functional Assessment of Cancer Therapy-Colorectal Cancer (FACT-C)									
Physical well-being	-	25.7±3.2	26.6±2.5	26.5±2.2	25.9±2.7	26.2±2.4	25.4±3.3	23.6±4.8	1,2,3,4,5>6
Social well-being	-	19.9±4.3	20.3±3.7	19.3±4.5	20.0±4.0	20.3±4.6	19.9±4.5	19.6±4.1	
Emotional well-being	-	21.3±2.9	22.0±2.3	21.5±2.1	21.3±3.1	22.0±2.3	20.8±3.4	20.5±3.4	1,4>6; 1,4>5
Functional well-being	-	18.9±4.4	19.9±4.0	19.2±3.2	19.1±5.1	19.7±3.7	18.7±4.2	16.5±4.8	1,2,3,4,5>6
Colorectal cancer subscale	-	21.8±3.1	22.3±2.9	22.2±2.2	21.8±2.8	22.3±3.1	21.2±3.4	20.9±3.8	1,4>6
Trial outcome index	-	66.4±8.8	68.8±7.2	67.9±5.9	66.8±8.5	68.2±7.6	65.2±9.1	61.0±11.2	1,2,3,4,5>6
FACT-G	-	85.9±10.7	88.7±8.7	86.6±8.9	86.4±10.8	88.3±9.0	84.7±11.7	80.2±12.3	1,2,3,4>6
FACT-C	-	107.6±12.7	111.0±10.2	108.8±9.9	108.2±12.8	110.6±11.0	105.8±13.8	101.1±15.0	1,2,3,4>6
Mean±SD SF-12 Health Survey									
Physical functioning	86.7±23.0	78.5±29.6	85.0±24.8	84.1±25.8	77.2±30.3	85.1±25.2	75.7±30.7	63.5±34.5	1,2,3,4>6
Role physical	77.6±24.1	76.2±27.6	85.3±21.8	80.9±22.0	76.7±28.8	82.8±23.5	74.1±26.4	55.9±32.8	1>5; 1,2,3,4,5>6
Bodily pain	73.1±26.0	86.7±22.9	88.2±20.6	92.8±16.3	87.2±19.9	90.7±20.4	83.5±25.5	78.9±29.2	2,4>6
General health	45.6±27.6	52.3±25.8	55.4±24.6	49.9±22.6	53.6±27.1	57.9±24.6	52.0±26.0	43.0±27.7	1,4>6
Vitality	62.0±25.1	67.2±19.7	71.2±17.9	69.7±18.9	66.6±22.5	72.2±16.7	65.1±18.0	57.9±22.1	1,2,4>6
Social functioning	79.4±24.9	81.5±28.6	92.1±18.2	84.8±26.3	81.3±27.4	88.6±24.0	78.7±29.4	61.5±34.7	1>5; 1,2,3,4,5>6
Role emotional	73.5±21.8	89.3±19.4	91.9±16.2	91.7±14.8	91.6±17.8	91.4±18.7	88.4±19.4	80.3±25.7	1,2,3,4>6
Mental health	67.9±19.0	79.6±15.6	80.4±14.0	80.1±13.0	81.4±16.3	80.8±15.3	78.9±15.8	75.8±18.5	
Physical component score	50.0±9.2	46.9±10.6	49.7±9.0	49.0±8.7	46.5±10.7	49.9±8.4	45.8±10.9	40.4±12.5	1,2,3,4,5>6
Mental component score	50.1±9.5	57.2±8.0	58.3±6.7	57.4±7.7	58.1±7.4	58.0±7.3	56.9±7.9	54.3±10.2	1,3,4>6
Mean±SD SF-6D Health Survey preference score	0.825±0.13	0.825±0.14	0.871±0.12	0.832±0.12	0.831±0.14	0.858±0.12	0.817±0.13	0.732±0.15	1,2,3,4,5>6

* Higher scores indicate higher levels of functioning or quality of life

† Significant difference between the six colorectal neoplasm stages by Tukey Post-hoc multiple comparisons

(12) annual I-FOBT plus sigmoidoscopy every 5 years (I-FOBT1+SIG5), and (13) annual I-FOBT plus sigmoidoscopy every 10 years (I-FOBT1+SIG10).

The cost-effectiveness analysis was performed using the TreeAge Pro Suite 2009 Release 1.0.2 (TreeAge Software, Williamstown [MA], US). Direct medical costs of CRN care from the health care provider perspective were used in the model. Data were extracted from a Hong Kong study[3] that estimated the local CRN costs for each stage of CRN. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental cost (ΔC) by the incremental effectiveness (ΔE) in terms of life-years (LY) and QALYs gained for a particular screening strategy compared with no screening.

TABLE 2. Clinical and socio-demographic factors associated with health-related quality of life (HRQOL) scores in colorectal neoplasm (CRN) patients (n=515) by multivariate linear regression

Independent variables	FACT-C total score		SF-12 physical component score		SF-12 mental component score		SF-6D	
	Coeff	SE (95% CI)	Coeff	SE (95% CI)	Coeff	SE (95% CI)	Coeff	SE (95% CI)
Constant	89.21*	4.41 (80.57, 97.85)	39.81*	3.78 (32.41, 47.21)	45.40*	2.87 (39.78, 51.01)	0.6436*	0.0478 (0.5500, 0.7372)
Clinical factors								
CRN stage (reference: stage IV)								
Low-risk polyp	9.47*	1.99 (5.57, 13.37)	8.44*	1.66 (5.19, 11.69)	3.82*	1.26 (1.35, 6.28)	0.1248*	0.0210 (0.0837, 0.1659)
High-risk polyp	7.10*	2.08 (3.03, 11.17)	8.02*	1.73 (4.63, 11.42)	2.14	1.31 (-0.44, 4.71)	0.0841*	0.0219 (0.0411, 0.1270)
Stage I	5.79*	2.04 (1.78, 9.79)	5.49*	1.70 (2.15, 8.83)	3.74*	1.29 (1.21, 6.28)	0.0903*	0.0215 (0.0481, 0.1326)
Stage II	8.02*	1.90 (4.28, 11.75)	8.91*	1.59 (5.80, 12.02)	3.10*	1.20 (0.74, 5.46)	0.1143*	0.0201 (0.0749, 0.1537)
Stage III	4.18*	1.84 (0.56, 7.80)	4.89*	1.54 (1.88, 7.91)	2.61*	1.17 (0.33, 4.90)	0.0760*	0.0195 (0.0379, 0.1142)
Months since diagnosis†	0.02*	0.01 (0.00, 0.04)	0.02	0.01 (0.00, 0.03)	0.00	0.01 (-0.01, 0.01)	0.0002*	0.0001 (0.0000, 0.0005)
Primary (reference: sigmoid)								
Colon	-1.04	1.45 (-3.87, 1.79)	-1.74	1.20 (-4.10, 0.62)	0.01	0.91 (-1.78, 1.80)	-0.0073	0.0152 (-0.0372, 0.0225)
Rectum	-1.25	1.43 (-4.05, 1.55)	-2.81*	1.19 (-5.14, -0.47)	-1.15	0.90 (-2.91, 0.62)	-0.0302*	0.0150 (-0.0597, -0.0008)
Family history of colorectal cancer	-0.95	1.39 (-3.67, 1.77)	0.36	1.16 (-1.91, 2.62)	-0.36	0.88 (-2.08, 1.36)	0.0047	0.0146 (-0.0240, 0.0333)
Chronic co-morbidities (present)	-0.74	1.24 (-3.17, 1.68)	-0.18	1.03 (-2.20, 1.84)	-0.30	0.78 (-1.84, 1.23)	-0.0090	0.0130 (-0.0346, 0.0165)
Socio-demographic factors								
Male	-0.24	1.26 (-2.71, 2.24)	0.42	1.05 (-1.64, 2.49)	2.06*	0.80 (0.49, 3.62)	0.0297*	0.0133 (0.0036, 0.0557)
Age†	0.22*	0.06 (0.10, 0.34)	0.04	0.05 (-0.06, 0.14)	0.16*	0.04 (0.08, 0.24)	0.0014*	0.0006 (0.0001, 0.0027)
Education (reference: tertiary)								
No formal schooling	0.51	2.41 (-4.21, 5.24)	-0.33	2.01 (-4.28, 3.61)	0.09	1.53 (-2.90, 3.08)	0.0026	0.0254 (-0.0472, 0.0525)
Primary	-0.49	1.91 (-4.23, 3.26)	0.40	1.59 (-2.72, 3.52)	-1.20	1.21 (-3.57, 1.17)	0.0056	0.0201 (-0.0339, 0.0450)
Secondary	0.44	1.76 (-3.01, 3.88)	-0.43	1.47 (-3.31, 2.44)	-0.23	1.11 (-2.40, 1.95)	0.0032	0.0185 (-0.0331, 0.0395)
Married	1.32	1.29 (-1.21, 3.84)	0.04	1.07 (-2.06, 2.15)	-0.09	0.82 (-1.68, 1.51)	0.0046	0.0136 (-0.0221, 0.0312)
Currently working	1.72	1.54 (-1.31, 4.75)	1.55	1.29 (-0.97, 4.08)	0.77	0.98 (-1.15, 2.68)	0.0311	0.0163 (-0.0008, 0.0630)
Household monthly income ≤HK$20000	-3.06	1.71 (-6.42, 0.30)	-1.89	1.43 (-4.69, 0.92)	-0.65	1.08 (-2.78, 1.47)	-0.0213	0.0181 (-0.0568, 0.0141)
Ever smoking	1.22	1.43 (-1.59, 4.03)	0.75	1.19 (-1.59, 3.09)	-1.11	0.91 (-2.89, 0.66)	0.0209	0.0151 (-0.0087, 0.0505)
Ever drinking	0.28	1.41 (-2.49, 3.05)	0.26	1.18 (-2.05, 2.57)	0.23	0.89 (-1.52, 1.98)	-0.0095	0.0149 (-0.0386, 0.0197)
R^2	**11.6%**		**11.9%**		**10.2%**		**14.8%**	
Adjusted R^2	**8.0%**		**8.3%**		**6.6%**		**11.3%**	

* P<0.05

† HRQOL scores change in coefficient for each unit increase in independent variable

Results

HRQOL of patients with colorectal neoplasms

Of the 553 subjects who completed the HRQOL evaluation at baseline, 479 (86.5%) and 414 (74.7%) completed the survey at 6 months and 12 months, respectively. The subjects' SF-6D preference scores were comparable with the Hong Kong general population norm, except for those with stage III and IV CRC (Table 1). There was a progressive decline in HRQOL and health preference scores from low-risk polyp to stage IV CRC. The FACT-C, SF-12v2 subscores of physical functioning, role physical, general health, vitality, social functioning, PCS, and SF-6D health preference scores were higher (but not significantly) in patients with stage II CRC than with stage I CRC and high-risk polyp.

Factors associated with HRQOL

Clinical and socio-demographic factors accounted for 11.6%, 11.9%, 10.2%, and 14.8% of the total variations, as indicated by R^2, in FACT-C total, PCS, MCS, and health preference scores of patients with CRN, respectively (Table 2). The health preference score was poorer in patients with rectal neoplasms but better in those diagnosed for a longer duration. The MCS and health preference scores were greater in males and older patients. Rectal neoplasms were associated with worse PCS compared to sigmoid neoplasms. The HRQOL score was not associated with chronic co-morbidities or a family history of colorectal cancer, or socio-demographic factors such as educational level, marital status, working status, household income, smoking status, and drinking status.

Cost-effectiveness of CRC screening strategies

The ICER in terms of LY and QALYs gain of each screening strategy was compared with that of no screening (Table 3). The most effective strategy in terms of LY gained and QALY gained was I-FOBT1 and I-FOBT1+SIG5, respectively. Compared with no screening, the most cost-effective strategy was I-FOBT2 at an ICER of HK$2 162 000 per LY gained, and HK$43 660 per QALY gained. Strategy I-FOBT1 was more effective than I-FOBT2 at a slightly higher ICER of HK$51 610 per QALY gained.

Discussion

Patients with CRC reported worse PCS but better MCS. The health preference of Chinese patients with CRN was comparable with that of the general population norm in Hong Kong, except for those with advanced (stage III and IV) cancers. Patients with rectal CRN tended to report poorer HRQOL, as

TABLE 3. Cost-effectiveness for each colorectal cancer screening strategy

Screening strategy*	Cost per person (HK$)	Effectiveness		Incremental cost-effectiveness ratio compared to control	
		Life years	Quality-adjusted life years	$1000/life years	$1000/quality-adjusted life years
No screening (control)	1507.50	15.93831	15.62478	-	-
G-FOBT1	21281.34	15.93953	15.75536	16256.42	151.43
I-FOBT1	13107.12	15.94238	15.84951	2851.50	51.61
G-FOBT2	11978.12	15.93924	15.70582	11241.73	129.20
I-FOBT2	9306.47	15.94192	15.80341	2162.08	43.66
SIG5	19369.06	15.94077	15.74849	7255.27	144.38
SIG10	11229.64	15.93957	15.69496	7697.89	138.52
COL5	24141.55	15.94217	15.79698	5869.72	131.44
COL10	14084.96	15.94065	15.73348	5380.46	115.70
G-FOBT1+SIG5	34923.60	15.94025	15.80462	17236.45	185.81
G-FOBT1+SIG10	29197.56	15.93981	15.77971	18393.31	178.72
I-FOBT1+SIG5	26169.89	15.94217	15.85910	6391.00	105.25
I-FOBT1+SIG10	20086.00	15.94221	15.85368	4760.06	81.16

* G-FOBT1 denotes annual guaiac faecal occult blood test (G-FOBT), I-FOBT1 annual human haemoglobin immunochemical-based FOBT (I-FOBT), G-FOBT2 biennial G-FOBT, I-FOBT2 biennial I-FOBT, SIG5 sigmoidoscopy every 5 years, SIG10 sigmoidoscopy every 10 years, COL5 colonoscopy every 5 years, COL10 colonoscopy every 10 years, G-FOBT1+SIG5 annual G-FOBT plus sigmoidoscopy every 5 years, G-FOBT1+SIG10 annual G-FOBT plus sigmoidoscopy every 10 years, I-FOBT1+SIG5 annual I-FOBT plus sigmoidoscopy every 5 years, and I-FOBT1+SIG10 annual I-FOBT plus sigmoidoscopy every 10 years

measured by the PCS and SF-6D preference scores. More attention should be paid to the rehabilitation of physical health for CRC survivors. The CRN stage at diagnosis was the most significant determinant of HRQOL and health preference, and indicates the importance of early detection of CRC. The SF-6D health preference scores by CRN stage would be useful for estimation of QALYs for cost-effectiveness analysis of interventions in CRN.

For the Chinese population in Hong Kong, strategy I-FOBT2 is the most cost-effective at an ICER of HK$43 660 per QALY gained, well below international thresholds of US$50 000[4] and GBP$20 000.[5] CRC screening strategies that utilised sigmoidoscopy, colonoscopy, or G-FOBT alone were dominated by strategies that include the I-FOBT for population-based screening of CRC in Chinese people. G-FOBT should no longer be the method of choice for CRC screening. Clinicians and health policy makers can take reference of these findings to develop evidence-based guidelines for CRC screening in the Chinese population of Hong Kong.

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Generalised cost-effectiveness analysis for breast cancer prevention and care in Hong Kong Chinese

IOL Wong *, JWH Tsang, BJ Cowling, GM Leung

KEY MESSAGES

1. A state-transition Markov model was used to evaluate various interventions across different breast cancer stages based on the generalised cost-effectiveness analysis.
2. From all strategies considered, the optimal allocation of additional resources for breast cancer in descending order would be: 25% reduction in waiting time for postoperative radiotherapy (average cost-effectiveness ratio, US$5000 per quality-adjusted life year [QALY]); enhanced, home-based palliative care (US$7105 per QALY); adjuvant, sequential endocrine therapy (US$17 963 per QALY); targeted immunotherapy (US$62 092 per QALY); and mass mammography screening for women aged 40 to 69 years (US$72 576 per QALY).
3. The generalised cost-effectiveness analysis for the full range of interventions for the same disease enables rational prioritisation and coherent allocation of resources.

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Introduction

Decisions on funding for interventions at different stages of specific conditions have often been made in isolation. For diseases such as breast cancer, budgetary allocation was proposed to be set at a higher level, given the local disease burden. We have used generalised cost-effectiveness analysis (GCEA)[1] to compare alternative breast cancer-related interventions throughout the disease course.[2] In the context of the Hong Kong public health care system, this study determined the optimal combination of screening, enhanced capacity for postoperative radiotherapy, adjuvant hormonal therapy with aromatase inhibitors (AIs), and targeted immunotherapy with trastuzumab (herceptin) [that has been excluded from the standard drug formulary in the public sector], and enhanced palliative services in order to maximise overall clinical benefits, subject to the constraints of a limited budget.

Methods

This study was conducted from September 2011 to August 2012. Data were extracted from local clinical, epidemiology and economic data, the US Surveillance, Epidemiology, and End Results database, and the literature and expert opinion whenever appropriate. Clinical effectiveness data from several breast cancer trials including the Early Breast Cancer Trialists' Collaborative Group overview of tamoxifen, the ATAC trial, and other primary breast cancer trials including NSABP (trial B-31), NCCTG (trial N9831), HERA, and BCIRG (trial 006) were also used. Cost data were derived mostly from local sources such as the government gazette (public fees and charges) and publications of the Hospital Authority (patient-related group costs). To verify internal and external data consistency, the derived cost estimates were benchmarked with relevant overseas' data.

Based on our previous decision analytic model for the clinical course of breast cancer for Hong Kong Chinese women (Fig 1),[3] the GCEA evaluated various interventions across different stages of breast cancer. The costs and benefits of alternative strategies were considered throughout the disease pathway (Fig 2). To identify the full range of possible interventions throughout the disease course, the literature on prevention and care of breast cancer appropriate for implementation in Hong Kong was reviewed. Relevancy of associated data to support a cost-effectiveness analysis was also considered.

Strategies studied were: (1) biennial mammography for women aged 40 to 69 or 79 years, (2) reduction in waiting time for postoperative radiotherapy by 15% or 25%, (3) neo-adjuvant treatment using newer and more expensive hormonal modulators AIs (such as anastrozole, letrozole, and exemestane) for postmenopausal hormonal-sensitive patients (upfront AI therapy or sequentially/switching with tamoxifen and AI), (4) targeted trastuzumab immunotherapeutics (ie

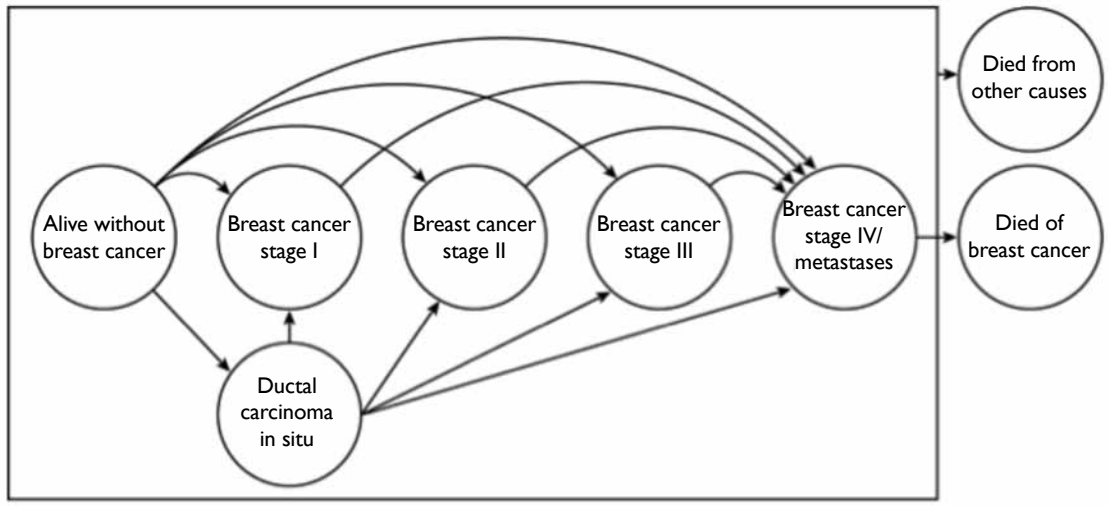

FIG 1. Health states and transitions, adopted from Wong et al, 2007[3]

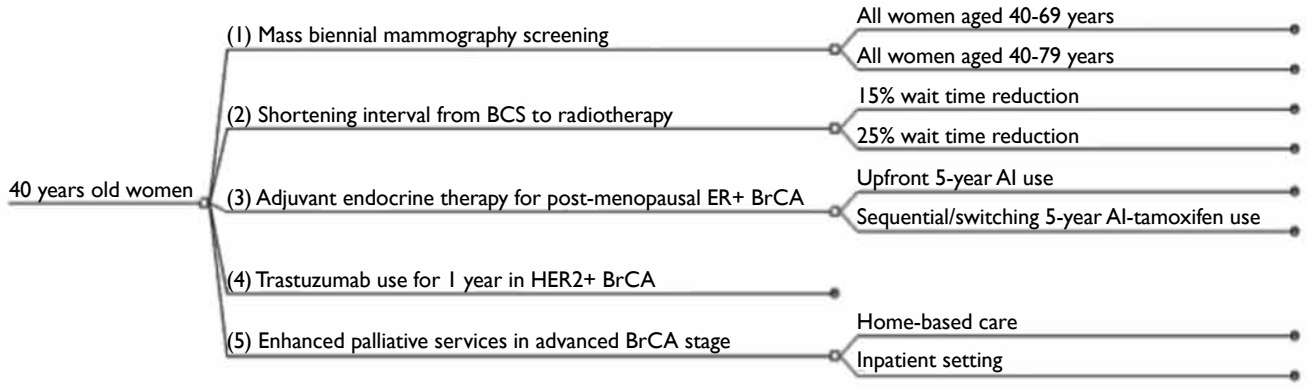

FIG 2. Decision tree of breast cancer–related interventions*

* BCS denotes breast-conserving surgery, AI aromatase inhibitor, ER+ oestrogen receptor positive, BrCA breast cancer, and HER2+ over-expression of human epidermal growth factor receptor 2

herceptin) for breast cancer patients with HER2 over-expression, and (5) enhanced home- or inpatient-based palliative services. The current standard and protocol of care as per the Hospital Authority (with comparably high international standards in management and patient care) was the comparator. Model parameters and assumptions were based on best available data including local clinical, epidemiological, and economic data, as well as a comprehensive literature review. The costs, quality-adjusted life years (QALYs) saved, and average cost-effectiveness ratios of all strategies were compared. Budgetary thresholds were benchmarked against hypothetical scenarios of different funding levels. Guidelines from the World Health Organization's WHO-CHOICE programme[1] were followed.

Five main direct medical costs were considered: (1) mammography screening, (2) evaluation of abnormal screens, (3) initial treatment of ductal carcinoma in situ and invasive cancer including diagnostic tests, procedures, surgery, drugs (standard formulary inclusive of tamoxifen), outpatient visits, and hospitalisation, (4) adjuvant hormonal AI therapy and immunotherapeutics (including trastuzumab, HercepTest, and FISH testing for HER2 expression, and cardiac monitoring), and (5) terminal care during the last 6 months of life. Other major non–health care costs were also considered such as transportation and time costs. All costs were adjusted to the 2010 level.

In the GCEA, the performance of alternative options of the same class of interventions (eg mass biennial screening for women aged 40 to 69 years vs 79 years) was first assessed under a 'competing choice' framework using the incremental cost-effectiveness ratio (ICER). Strategies that were less effective and more costly than an alternative strategy (strongly dominated) and strategies that had a higher ICER than a more effective alternative strategy (weakly dominated) were eliminated. This process was repeated for all classes of intervention where more than one alternative was considered. All strategies that remained from different classes of interventions were entered into a generalised league table and compared based on their average cost-effectiveness ratios. Independent interventions can be added to existing interventions, whereas mutually exclusive interventions must replace an existing intervention. Results of the interventions were then rank-ordered by their average cost-effectiveness ratios in the same league table.

Detailed clinical data, parameters, and model assumptions have been reported.[2] A societal perspective was adopted in the analyses. Future costs and QALYs were discounted at a rate of 3% per year.

A probabilistic sensitivity analysis was conducted to examine uncertainty surrounding choice of policy. Clinical and cost parameters were specified with appropriate probabilistic distributions, and cost-effectiveness results associated with selecting values at random from the distributions were entered in a Monte Carlo simulation of the model with 1000 runs. Cost-effectiveness acceptability curves were constructed to present the uncertainty of the ICER across different values of the decision thresholds or ceiling ratios that represents acceptable willingness-to-pay thresholds.

Results

For the Hong Kong female population aged ≥40 in 2009 (accounting for 1 961 000), the incremental total annualised costs, QALYs saved, and average cost-effectiveness ratio of different strategies were compared (Table). The optimal allocation of additional funding for breast cancer in descending order would be: (1) 25% reduction in waiting time for postoperative radiotherapy (US$5000/QALY); (2) enhanced home-based palliative care (US$7105/QALY); (3) adjuvant sequential endocrine therapy (US$17 963/QALY); (4) targeted immunotherapy (US$62 092/QALY); and (5) mammography screening for women aged 40 to 69 years (US$72 576/QALY).

In the probabilistic sensitivity analyses, the first three interventions were certain to be cost-effective at the conventionally adopted threshold of US$50 000 per QALY saved (Figure not shown).

Assuming an additional annual expenditure for breast cancer screening, diagnosis, and treatment in Hong Kong totalling about US$6.1 million, strategies including 25% reduction in waiting time for postoperative radiotherapy plus enhanced home-based palliative care should be adopted, thereby yielding 902.1 additional QALYs overall. If an additional US$30 million were available, in addition to the above two strategies, sequential endocrine adjuvant therapy should also be adopted on a partial basis.

Discussion

Comparing cost-effectiveness of different strategies throughout the course of breast cancer provides a

TABLE. Generalised cost-effectiveness analysis for 1 961 100 Hong Kong Chinese women aged ≥40 years

Strategy	Lifetime costs (million 2010 US$)*	Lifetime quality-adjusted life years (QALYs) saved*	Average cost-effectiveness ratio (US$ per QALY saved)	Cumulative costs (million 2010 US$)	Cumulative QALYs saved
25% reduction in waiting time for postoperative radiotherapy (for women with stage I-II breast cancer)	0.8	156.9	5000	0.8	156.9
Enhanced home-based palliative care (for women with advanced cancer stages)	5.3	745.2	7105	6.1	902.1
Providing an aromatase inhibitor for 2 to 3 years followed by tamoxifen (for women with postmenopausal oestrogen receptor positive cancer)	38.0	2118.0	17 963	44.1	3020.1
1-year trastuzumab use (for women with HER2 over-expressed cancer)	448.1	7216.8	62 092	492.2	10 236.9
Biennial mammography for women aged 40 to 69 years	4879.0	67 226.5	72 576	5371.3	77 463.5
Incremental from biennial mammography for women aged 40 to 69 years to women aged 40 to 79 years	721.7	3530.0	204 444	6092.9	80 993.4

* Compared with the status quo scenario, which is the current standard and protocol of care as per the Hospital Authority

holistic value-for-money understanding of the full range of interventions, and thus enables rational prioritisation and coherent allocation of resources. The findings may also have implications for affordability of cancer medicines in the Hong Kong public health care system, and for societal values and financial consequences for patients and their families.

Of the additional interventions not currently covered in the public sector, mass mammography screening would be the least cost-effective, compared with a reduction in waiting time for postoperative radiotherapy, palliative services, or adjuvant endocrine and immunotherapy. This finding is consistent with two previous local studies: (1) a conventional cost-effectiveness analysis of mass mammography reported that the ICER was above that of broadly accepted thresholds,[3] and (2) a GCEA of colorectal, cervical, and breast cancer screening in women suggested that routine regular mammography would be the least cost-effective compared with colonoscopy and cervical smears +/- human papillomavirus testing (ie the only other preventive screening programmes for common cancers in women).[4] Underlying these findings is the relatively lower (albeit increasing)[5] risk of breast cancer in Hong Kong Chinese women,[3] compared with their western counterparts. A lower incidence would mean a lower prevalence of disease at the time of screening, which in turn affects the performance of the mammography when evaluated at the population level. Any potential benefit of earlier detection in a low-risk population would be outweighed by the corresponding potential risk/harm induced by over-diagnosis, false positive screens, false reassurance, anxiety and psychological consequences.[3] Screening the entire population would be very costly, where the benefits only accrue to a small number of women who develop cancer. The effectiveness of mammography screening would depend on the prevalence of undiagnosed disease. The effectiveness of cancer treatment would be largely similar across different populations.

A potential caveat was that the assumption of perfect adherence to the interventions does not fully reflect the inherent heterogeneities and complexities of disease type, service delivery, individual behaviour, and patient preferences. The optimised benefits projected in our model may not be completely realised.

Given the current disease pattern and age profile of patients in the Hong Kong Chinese female population, the most cost-effective interventions are those that ensure women receive the most-intensive treatment and care after a diagnosis of breast cancer, rather than receive mammography screening at a younger age. Further studies are needed to understand how these decisions can be flexibly deployed to comply with various budgetary constraints, affordability of cancer medicines, and ethical considerations. Our results can further inform policy debates about resource allocation for service delivery regarding breast cancer prevention, diagnosis, treatment, and palliative care.

Acknowledgement

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Cost-effective osteoporosis intervention thresholds for Hong Kong postmenopausal women

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KEY MESSAGES

1. A Markov state-transition model was used to determine osteoporosis treatment thresholds in osteoporotic Hong Kong postmenopausal women, using local data of hip, vertebral, and wrist fracture incidence and mortality.
2. The lifetime costs and quality-adjusted life years (QALYs) for the treated (osteoporosis treatment for 5 years) and untreated cohorts were estimated from a societal perspective.
3. The incremental cost-effectiveness ratio for treatment in women around age 50 years was estimated to be approximately HK$3.6 million per QALY. This decreased with increasing age and fell below the cost-effectiveness threshold of $333 840 from the age of 70 years.
4. Probabilistic sensitivity analysis showed that treatment for those aged ≥70 years had a 75% likelihood of being cost-effective, even at a QALY value of only about $250 000.
5. The cost-effectiveness model can be used together with the World Health Organization fracture risk assessment algorithm to determine whether treatment is likely to be cost-effective at a given QALY value for any individual.

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Introduction

Osteoporosis is characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[1] Osteoporosis is more common in older people, and complications of fragility fractures are associated with high morbidity and mortality. Although there was a slight decline in the age-specific incidence of hip fracture from 1995 to 2004 in Hong Kong, the absolute number of hip fractures has increased due to an ageing population.[2] In 1996, the cost of acute hospital care for hip fractures exceeded 1% of the public hospital budget. Sensitive fracture risk assessment tools can improve the prognostication of osteoporotic fracture and result in significant health care savings.

The intervention threshold for osteoporosis should be based on the absolute risk rather than the relative risk of fracture based solely on the bone mineral density (BMD) T-score. Apart from BMD assessment, global evaluation of osteoporotic fracture risk can be enhanced by incorporation of clinical risk factor (CRF) assessment. We have identified eight independent CRFs for osteoporotic fracture in Hong Kong postmenopausal women. Some are related to the risk of fall; others are related to osteoporosis and low BMD.[3] The World Health Organization fracture risk assessment algorithm (FRAX) provides 10-year probabilities of hip fractures and major osteoporotic fractures (of the spine, hip, humerus, and forearm). The FRAX integrates independent CRFs for osteoporotic fracture, including low body mass index, parental history of hip fracture, history of fragility fracture, long-term use of oral glucocorticoids, rheumatoid arthritis, other secondary causes of osteoporosis, current smoking, and an average intake of alcohol ≥3 units per day.[4]

Integration of these CRFs and the BMD T-score in the FRAX model not only increases its sensitivity to detect those at high risk of fracture over the subsequent 10-years, but also provides the basis on which intervention thresholds can be developed. This study aimed to determine intervention thresholds for osteoporotic fractures (based on the absolute 10-year risk) in Hong Kong postmenopausal women, using the local epidemiology and economics (fracture incidence, morbidity, mortality, and costs).

Methods

This study was conducted from October 2009 to November 2011. A cost-effectiveness model was used to simulate the transition between no fracture, fracture, and post-fracture states, and the appropriate

costs and quality-adjusted life years (QALYs) over the remaining lifetime in women of different ages. By comparing women with or without osteoporosis treatment, the difference in costs and QALYs gained through treatment was used to estimate the cost-effectiveness of treatment at different ages at different fracture rates. A treatment that gained a QALY at a cost equivalent to under two times the per capita gross domestic product is considered cost-effective.

A Markov cohort state-transition model was used to simulate osteoporosis treatment thresholds in Hong Kong postmenopausal women. The model was based on a Swedish cost-effectiveness model for osteoporosis treatment published in 2004.[5] This model began with women in the no fracture state and simulated the yearly transition from age 50 to 100 years or death. The state transition probabilities were based on local age-specific mortality and estimated fracture incidence.

Age-specific hip fracture incidence for postmenopausal women in Hong Kong in 2004 was obtained from the Clinical Data Analysis Reporting System of the Hospital Authority. Age-specific mortality was obtained from the Hong Kong Government Census and Statistics Department. Estimated excess mortality in the first year following hip fracture was based on the mortality risk ratio for hip fracture in Swedish women and Hong Kong mortality. For treatment effect, we assumed that 5 years of drug treatment would reduce the risk of all osteoporotic fracture by 35%. This treatment effect was assumed to decline linearly over 5 years after the end of treatment.

The long-term outcome of treatment was determined using QALYs. The age-related health state for females from a US study and the utility scores for different types of fracture from a Swedish study were used to estimate the disutility of a fracture at a specific age by multiplying the associated health state value of the age group by 1 minus the disutility from the fracture. Using the same assumption to the US study, we assumed that disutility from a fracture would decline linearly over 5 years after the fracture event and that there would be no further disutility in the post-fracture state thereafter.

Costs were based on a societal perspective and adjusted to the year 2009 level. The cost of a fracture included the direct medical costs in the first year and, where relevant, the cost of a nursing home in subsequent years, and the indirect costs of productivity loss due to the fracture. The mean length of stay in hospital in those with a fracture was estimated using the admission data for 2004 from the Hospital Authority. We assumed that 50% of hip fracture patients would be admitted to a nursing home. Productivity loss in the first year was calculated by multiplying the recovery time by the median monthly income. The cost of the treatment included the costs of drugs and monitoring.

To estimate the cost-effectiveness of osteoporosis treatment, we first estimated the lifetime costs and QALYs for women with or without 5 years of drug treatment. All future costs and health effects were discounted at 3% per year. Incremental cost-effectiveness ratios (ICER) between the treated and untreated cohorts were calculated by dividing the difference in cost by the difference in QALYs. The ICERs were compared with the willingness-to-pay threshold for a QALY. Treatment was considered cost-effective if the ICER was below the willingness-to-pay threshold.

One-way sensitivity analyses were conducted to identify the parameters with the strongest effect on cost-effectiveness. In each analysis, one parameter was tested with different values while the other parameters remained unchanged. Probabilistic sensitivity analysis was conducted using second-order Monte Carlo simulation that selected random

TABLE 1. Cost-effectiveness analysis

Age (years)	Mean 10-year fracture risk (%)			Mean cost (HK$)		Incremental cost (HK$)	Mean quality-adjusted life years (QALYs)		QALY gain	Incremental cost-effectiveness ratio (cost/QALY) [HK$]*
	Hip	Vertebral	Wrist	Untreated	Treated		Untreated	Treated		
50	0.18	0.09	0.72	17 299	26 066	8767	17.231	17.234	0.002	3 580 206
55	0.47	0.10	1.02	19 861	28 370	8509	15.583	15.587	0.005	1 881 507
60	1.06	0.12	1.26	22 496	30 683	8188	13.731	13.738	0.008	1 055 436
65	2.47	0.18	1.37	25 003	3731	7728	11.812	11.827	0.015	518 322
70	5.44	0.30	1.55	28 070	34 529	6459	9.780	9.808	0.028	232 705
75	9.90	0.38	1.84	30 595	35 182	4587	7.904	7.949	0.045	101 200
80	16.14	0.36	1.96	30 915	33 315	2400	6.062	6.124	0.063	38 229
85	19.01	0.32	1.74	29 845	30 043	198	4.630	4.696	0.067	2974

* The extra cost to gain one extra QALY after treatment, compared with no treatment

values from the distribution of each parameter. Results are presented as cost-effectiveness acceptability curves.

Results

The ICER for drug treatment for women around age 50 years was estimated to be around HK$3.6 million per QALY. This decreased with increasing age and fell below the cost-effectiveness threshold of $333 840 from the age of 70 years (Table 1).

Table 2 shows the relative risk and the absolute 10-year risk of fracture for each age at which treatment becomes cost-effective. For example, the absolute 10-year risk of hip fracture at which it would be cost-effective to treat a 50-year-old woman would be 1.79, which is derived from a relative risk of 10.09, compared with the average risk in her age group of 0.18%. It is still cost-effective to treat a woman aged ≥85 years who has a relative risk of only 0.26 compared with her peers, which is 74% less than the average risk for that age group. This woman would have an absolute 10-year risk of hip fracture of 5.07%, compared with the average risk of 19.01% for this age group.

The probabilistic sensitivity analysis showed that at the cost-effectiveness threshold of HK$334 000, treatment for women aged ≥70 had a 75% likelihood of being cost-effective. This high likelihood of cost-effectiveness remained even at a QALY value of only about $250 000 (Fig). In addition, treatment for those aged 50 to 59 years was unlikely to be cost-effective on average, and for those aged 65 years it only reached a 50% or higher chance of being cost-effective if the value of a QALY gained exceeded HK$540 000.

TABLE 2. Estimated relative risk (RR) and absolute risk of fracture at which treatment becomes cost-effective

Age (years)	RR of fracture	10-year absolute risk of fracture (%)		
		Hip	Vertebral	Wrist
50	10.09	1.79	0.87	7.18
55	5.06	2.35	0.49	5.11
60	2.88	3.06	0.33	3.59
65	1.49	3.68	0.27	2.04
70	0.75	4.09	0.23	1.17
75	0.43	4.29	0.17	0.81
80	0.30	4.95	0.12	0.62
85	0.26	5.07	0.09	0.49

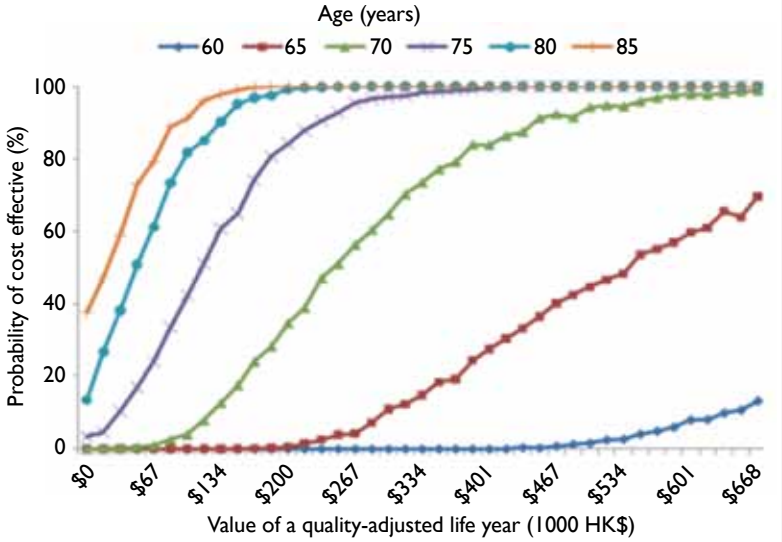

FIG. Cost-acceptability curves

Discussion

This cost-effectiveness model was used to determine the cut-off point for treatment based on treatment efficacy, impact on utility and hence QALYs gained, cost of treatment, and risks in the population. When used with the FRAX algorithm, it can determine whether a treatment is cost-effective at a given QALY value for any individual. This QALY value is open to debate. The cost-acceptability curve shows how the likelihood of cost-effectiveness varies according to the value of the outcome, and the model can be updated with new data and estimates when available.

There were some limitations in the present study. The data on incidence of fracture in Hong Kong were limited, especially those for vertebral and wrist fractures. The base case used estimates from Sweden, but in Asians vertebral fractures may be more common than hip fractures, and the ratio of vertebral to hip fractures was not known. Therefore, more solid data on vertebral fracture rates should have been obtained. The model only simulated hip, vertebral, and wrist fractures and ignored any other fractures. It was assumed that only one fracture would occur in any year. These may have led to underestimation of benefits. When a fracture was treated, the model assumed the subject would be 100% compliant with the treatment regimen. The utility scores used in the model were taken from overseas because of a lack of local data. Nonetheless, in the sensitivity analysis, substituting the utility scores from a systematic review made almost no difference to the results. This model was applied to women only. To adapt it to men, male data on fracture rates, mortality rates, and utility scores are required.

Conclusion

The cost-effectiveness model can be used with estimates of absolute risk of hip fracture from the

FRAX algorithm to determine the cost-effectiveness of drug treatment for women at different ages.

Acknowledgement

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Predicting postoperative cardiac complications using automated endothelial function test

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KEY MESSAGE

For patients undergoing non-cardiac surgery, non-invasive assessment of endothelial function provides additional predictive value, beyond clinical variables, for preoperative risk stratification of postoperative myocardial ischaemia and major cardiac complications.

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Background

Perioperative myocardial ischaemia is a common complication after non-cardiac surgery,[1] and is associated with severe morbidity and mortality.[2,3] The vascular endothelium is an important component in coronary artery disease.[4] Endothelial dysfunction may play an important role in perioperative myocardial injury, and its rapid assessment may enable cardiac risk stratification prior to surgery.[4] Based on an automated, non-invasive test to quantify reactive hyperaemia in response to brief upper limb ischaemia, a prospective observational cohort study was performed to determine the performance of preoperative endothelial function testing in predicting cardiac complications after non-cardiac surgery. Results of the study have been published.[5,6]

A representative sample of patients, at intermediate-to-high risk for postoperative cardiac complications, scheduled to undergo non-cardiac surgery were recruited.[5,6] Endothelial function was measured using an EndoPAT device (Itamar Medical, Caesarea, Israel). A reactive hyperaemia index (RHI) was calculated to indicate endothelial dysfunction (Fig). Blood samples were collected on the first 3 days after surgery for the measurement of plasma concentration of cardiac troponin T.

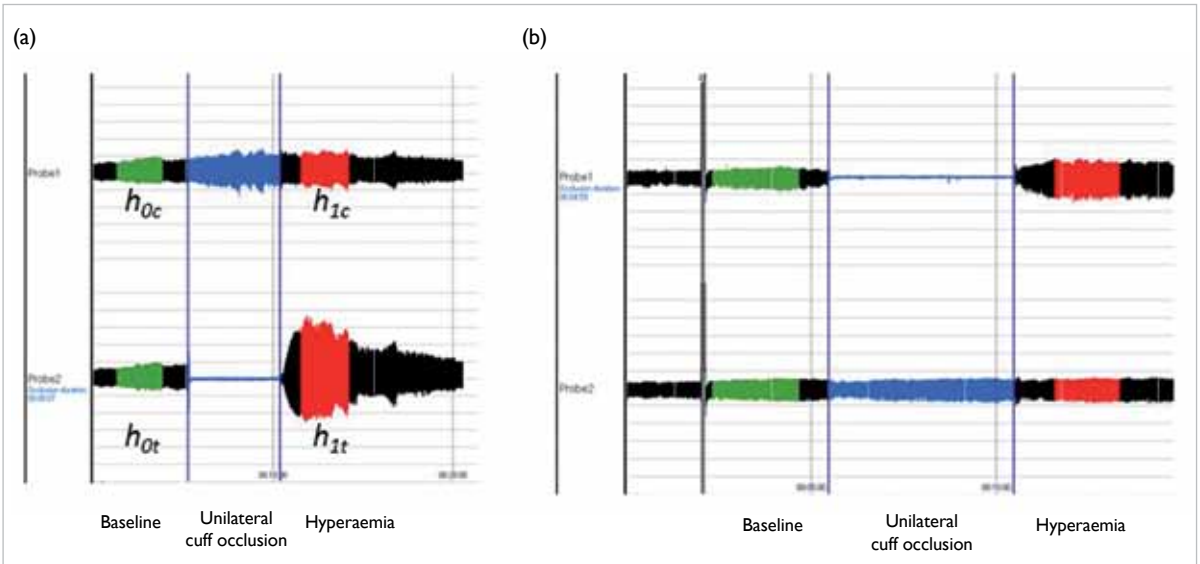

FIG. (a) Pulse amplitude tracing with normal endothelial function: during hyperaemia of a finger, baseline pulse amplitude is recorded. During cuff inflation, arterial flow is occluded and rapidly rises after release during the hyperaemic period. In the contralateral control finger, flow continues throughout, and pulse amplitude change is minimal. The reactive hyperaemic index (RHI) is a ratio of mean amplitude in the test finger during hyperaemia and that in baseline after adjusting for the change in the control finger, ie RHI=$(h_{1t}/h_{0t})/(h_{1c}/h_{0c})$. The calculated RHI for this tracing is 2.41. (b) In a patient with endothelial dysfunction, change in pulse amplitude is little in both the test and control fingers (RHI=1.15).

The primary endpoint was perioperative myocardial necrosis indicated by an elevation of cardiac troponin concentration of >0.03 μg/L.[2] The occurence of major adverse cardiac complications (including myocardial infarction, non-fatal cardiac arrest, stroke, pulmonary embolism, congestive heart failure, and new clinically significant atrial fibrillation), coronary intervention, and all-cause mortality within 30 days after surgery were recorded.

In this cohort, the mean duration of surgery was 3.8 (standard deviation, 1.7) hours. The median RHI was 1.51 (interquartile range, 1.34-2.08). By postoperative day 3, 10.6% of patients had a peak cTnT concentration of >0.03 μg/L, indicating occurrence of perioperative myocardial injury. At day 30, 8.2% had major cardiac complications. Taking RHI of ≤1.22 as the threshold, the area under receiver operating characteristic (ROC) curve was 0.89 (95% confidence interval [CI], 0.81-0.96), with sensitivity and specificity of 65% and 95%, respectively. Using the revised cardiac risk index of ≥2, the area under the ROC curve was 0.75 (95% CI, 0.64-0.86), with sensitivity and specificity of 82% and 65%, respectively.

Patients with endothelial dysfunction reported higher rates of perioperative myocardial injury (P=0.001) and 30-day postoperative cardiac complications (P=0.001). After adjustment for age, clinical risk score, and extent of surgery, endothelial dysfunction remained a significant risk factor for adverse cardiac outcomes. The population attributable risk analysis suggested that 41.8% of perioperative myocardial necrosis and 45.3% of postoperative cardiac complications were related to the presence of endothelial dysfunction. After adjustment for age, clinical risk factors, and extent of surgery, patients with endothelial dysfunction were less likely to be discharged from hospital on any given day after surgery than those with preserved endothelial function (hazard ratio=2.56; 95% CI, 1.53-4.17; P=0.001). Interestingly, RHI did not predict the development of acute kidney injury (odds ratio=1.60; 95% CI, 0.40-1.70; P=0.530).[5]

Conclusions

The study demonstrated the potential utility of non-invasive automated measure of endothelial dysfunction to provide rapid preoperative risk stratification (when used alone or combined with clinical risk score) for perioperative myocardial ischaemic injury in patients undergoing non-cardiac surgery. The RHI, however, did not predict postoperative acute kidney injury.

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Projecting ischaemic heart disease mortality and morbidity in Hong Kong

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KEY MESSAGES

1. No ischaemic heart disease (IHD) epidemic is forecast for Hong Kong, despite increasing exposure to risk factors. The IHD morbidity and mortality are projected to decline continuously until at least 2020.
2. Social disparities in IHD mortality are widening, particularly among women, partly because IHD is declining by generation for high-income women but not for low-income women. Differential exposure throughout life contributes to disparities in IHD that may be difficult to reverse in a short-time frame.

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Introduction

Ischaemic heart disease (IHD) is becoming a leading cause of morbidity and mortality in Hong Kong. Premature IHD is common in men. This study aimed to assess the relative contribution of age, period of IHD, and birth cohort effects to IHD mortality in women and men by socio-economic status, and to project mortality and morbidity from IHD in Hong Kong until 2020.

Methods

This study was conducted from December 2010 to November 2011. According to the International Classification of Diseases (ICD) codes, IHD is defined as ICD-8 410-414, ICD-9 410-414, and ICD-10 I20-I25. Sex-specific IHD death data and mid-year population figures by small area of residence for years 1976-2006 were obtained from the Hong Kong Death Registry and the Census and Statistics Department, respectively. There are about 280 Tertiary Planning Units (TPUs) in Hong Kong. The TPU boundaries are regularly updated to reflect population dynamics. Sparsely populated TPUs are merged with nearby TPUs so that approximately 200 TPUs are available for analysis.

For each TPU, median household income for 1976-2010 was obtained, as was information on migrant status (born in Hong Kong or elsewhere). All deaths associated with IHD were included. The mortality data were grouped into ten 5-year age-groups from 30-34 years to ≥75 years, and population data were grouped into six 5-year time periods from 1976-1980 to 2001-2005. This classification resulted in 15 birth cohorts.

Aggregated data for sex- and age-specific inpatient bed-days associated with IHD (ICD-9 410-414) from 1999 to 2009 were obtained from the Hospital Authority. The socio-economic status was classified as high- or low-income group based on the above or below median household income per capita of the TPU of residence for each year of observation, rather than using one inflation-adjusted cut-point throughout the period, to avoid classifying most people from early years as low income and most people from later years as high income.

Community burden in women and men associated with IHD by socio-economic status was obtained from population representative studies in Hong Kong, which have asked specifically about doctor-diagnosed IHD, using the Rose angina questionnaire.[1] These include the 1995 Cardiovascular Risk Survey.[1] Given that these cross-sectional studies were conducted over 10 years ago, we examined whether the ratio of IHD mortality to community burden of IHD has changed to take into account improvements in IHD treatment, which may have reduced the IHD case fatality.

Using an age-period-cohort (APC) Poisson model,[2] sex-specific IHD mortality over the past 30 years was decomposed into the effects of age at death, period of IHD at death, and cohort of birth by low/high income group. The effect of each of these components was projected separately in the Hong Kong population to give an overall forecast for IHD mortality from 2006 until 2020. Future hospital bed use and community burden was forecast, using the current ratio of IHD mortality to IHD hospital bed use and to the community burden of IHD. Whether migrant status may affect IHD mortality and morbidity was also investigated.

The second and the penultimate periods and the central birth cohort were used as reference to generate identifiable estimates for birth cohort and

period effects, respectively. Bayesian inference was used to estimate the model parameters, and the fitted model was used to project future mortality in three further 5-year periods up to 2015-2020. For the age, period of IHD, and cohort effects, second-order Gaussian autoregressive priors were specified in the forward direction. These priors specified that the initial expected value of each effect was based on an extrapolation from its two immediate predecessors. Three additional period and cohort effects were extrapolated to enable projections of future incidence. The model parameters were estimated using Markov Chain Monte Carlo simulations with five concurrent chains started at different initial values, because comparison of multiple chains enables discerning of convergence. The parameter estimates and derived rates were summarised in terms of posterior means and 95% confidence intervals.

To examine whether the results differed by socio-economic status or migrant status, we investigated any potential difference in birth cohort, calendar period or chronological age effects for men or women by stratifying our original set of analyses if appropriate by socio-economic status or migrant status.

Age-standardised IHD mortality was projected by sex or socio-economic status in the short to medium term. The uncertainty associated with projections was also assessed. In addition, join point regression was used to evaluate whether there has been any change in the trends in cohort and period effects over time and when change occurs (whenever applicable).[3] The best join point model selection method was based on Bayesian Information Criterion where the best model was selected with the smallest Bayesian Information Criterion.[3]

Future IHD morbidity (as public hospital use and community burden) was estimated in the short- to medium-term, based on the current age- and sex-specific ratios of IHD mortality to IHD hospital bed-use and IHD community burden. Data on private hospital use associated with IHD are difficult to obtain, but public hospitals account for 95% of all bed days in Hong Kong, so that projections based on the public sector only were appropriate and sufficiently accurate for planning purposes. Specifically, a study of acute myocardial infarctions at all hospitals in Hong Kong reported that 96.7% of cases were treated in the public sector.

Results

Age-standardised mortality by income group

The IHD mortality was higher among high-income men than low-income men in the early period and declined faster for the high-income group than the low-income group. From 2006-2010 to 2015-2020, the IHD mortality is projected to decline in the high-income group, but less so for the low-income group (Table).

Age, period, and birth cohort effects on trends in IHD mortality in women and men by socio-economic status

Parameter values of age, period, and cohort components with projections were estimated (Fig 1). Because of the known identifiability problem of APC models, where there was inherent linear independence between the three component effects (ie, birth cohort = period of deaths – age at death), only second-order changes (ie inflection points or changes in slopes) were interpretable. Among men and women, the mortality increased with age in the two income groups. There was also an acceleration at the age approximately after 50 years. There was a higher risk of mortality for the low-income group than the high-income group, particularly among older age-groups.

Relative risks were estimated for the fifteen 10-year birth cohorts beginning in the calendar year 1899 and the six 5-year time periods from 1976 to 2005 (Fig 2). Cohort effects dominated, and inflection points could be identified, while there were less apparent second-order changes in period effects. Regarding the cohort effects, there was a downturn in the 1920s for women in both income groups. In contrast for men, there was an earlier downturn followed by an upturn in the cohort effect around 1945 (ie for the first generation largely born in Hong Kong). The downward effect by cohort appeared to either start in an earlier generation for the high-income group than for the low-income group, or the downturn was more marked for the high-income group than the low-income group. In the join point analyses, the join points identified were consistent with the inflection points described above. With regard to the period effects, downward period effects in the early 1990s and upward period effects in the late 1990s were more evident for the low-income than the high-income group. Similar results were found in join point analyses for high-income men and women.

TABLE. Projected age-standardised ischaemic heart disease (IHD) mortality by income group from 2006 to 2020

Period for projection	Projected IHD mortality per 100 000 (95% CI)	
	Low-income group	High-income group
Female		
2006-10	24.9 (19.2-31.6)	16.0 (14.9-17.2)
2011-15	19.7 (10.8-31.6)	10.9 (9.6-12.3)
2016-20	19.7 (5.9-33.5)	7.9 (6.8-9.0)
Male		
2006-10	45.5 (36.6-55.3)	34.2 (32.7-35.8)
2011-15	41.0 (25.3-61.5)	29.5 (27.5-31.6)
2016-20	41.2 (17.1-74.1)	26.5 (24.2-29.4)

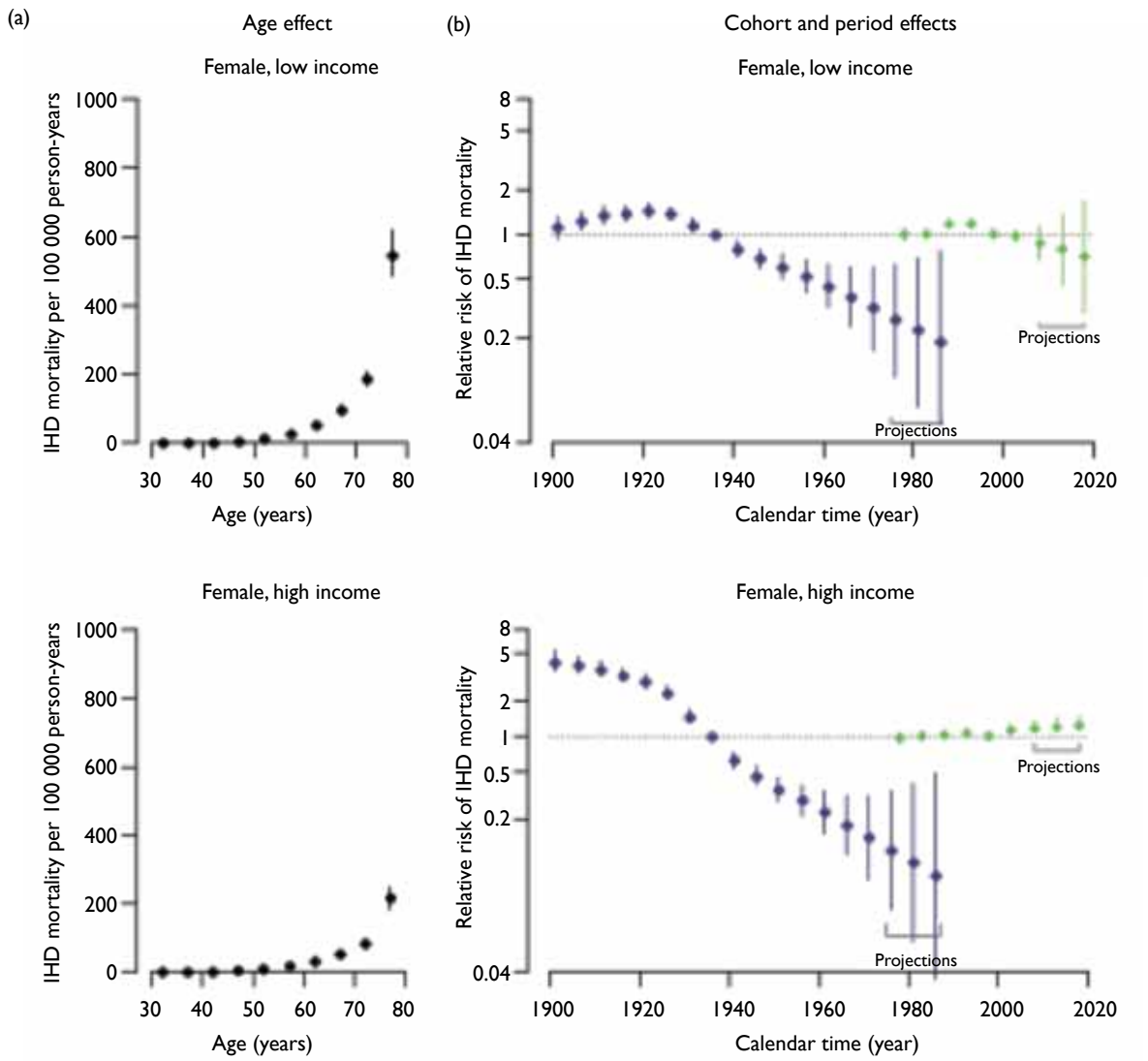

FIG 1. For women (DIC=453.604 for low-income group, DIC=443.02 for high-income group), (a) estimated age-specific annual ischaemic heart disease (IHD) mortality, and (b) estimated relative risks for 10-year birth cohorts and 5-year calendar periods, including projected cohort effects for birth cohorts centred on the years 1978, 1983 and 1988 and projected period effects for periods centred on the years 2008, 2013, and 2018

Discussion

In Hong Kong, there was no evidence of an emerging epidemic of IHD among men. The IHD mortality for both sexes was declining over the period. There was an upturn in the cohort effect for men for the first generation born in Hong Kong, but this was offset by other changes, so that the net change was still a decline, albeit a smaller decline than for women. It may seem counter-intuitive that IHD mortality is projected to decrease when many IHD risk factors (such as diabetes) are likely to increase as the lifestyle becomes more sedentary and westernised. The Framingham score substantially over-predicts the absolute risk of IHD in China.[4] The Framingham score is based on risk factors, not causal factors. The items in the Framingham score may correlate better with the underlying causal factors in some populations than others.

In contrast, with the somewhat unexpected findings of a lack of an epidemic of IHD among men, social inequality in IHD is widening. This reversal may be connected with a cohort effect, with corresponding implications for reversibility in a short-time frame.

The period effects were more marked for the low-income group, which is more sensitive to population-wide changes, such as the establishment of the Hospital Authority that coincided with a more marked downturn for the low-income group, and the Asian financial crisis in 1997 that coincided with a more marked upturn for the low-income group.

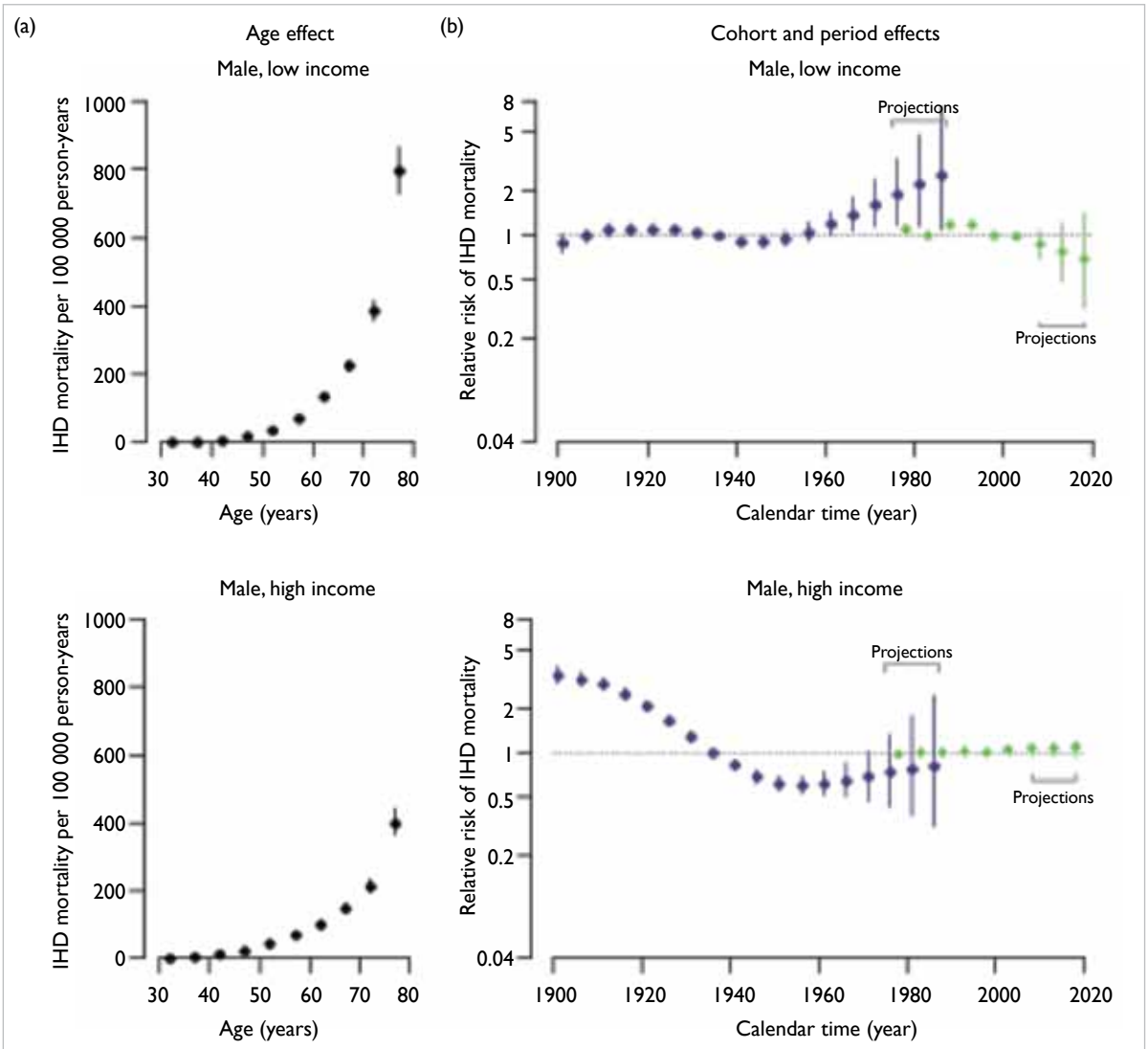

FIG 2. For men (DIC=526.797 for low-income group, DIC=569.726 for high-income group), (a) estimated age-specific annual ischaemic heart disease (IHD) mortality, and (b) estimated relative risks for 10-year birth cohorts and 5-year calendar periods, including projected cohort effects for birth cohorts centred on the years 1978, 1983 and 1988 and projected period effects for periods centred on the years 2008, 2013, and 2018

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Association of infant growth and pubertal adiposity: implications for future cardiovascular health and immunological benefits

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KEY MESSAGES

1. In the Children of 1997 birth cohort, faster infant growth was associated with higher body mass index (BMI) and waist circumference, but not waist-to-hip ratio at age 13 years.
2. Higher BMI among adolescence with faster infant growth may partially be attributed to a heavier frame and greater muscle mass rather than greater fat mass.
3. Fast growth in the first year of life was not associated with a lower risk of infectious morbidity.

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Introduction

Cardiovascular diseases are the leading cause of death in the world. Infancy is a key window of developmental plasticity and intervention, but the role of foetal and infant growth in cardiovascular disease remains controversial. We have reported a positive association of infant growth with body mass index (BMI) at age 7 years,[1] in the Children of 1997 birth cohort in Hong Kong.[2] Nonetheless, BMI in childhood may not track into adulthood and represents an unknown combination of muscle mass and fat mass. This study aimed to use the same birth cohort to clarify the association of infant growth with adiposity in adolescence in terms of both BMI and waist ratios, and to assess the association of infant growth and hospital use due to infections.

Methods

Children of 1997 birth cohort

The Children of 1997 birth cohort[2] is a population-representative Chinese birth cohort (n=8327) that covered 88% of all births in Hong Kong from 1 April 1997 to 31 May 1997. Families were recruited at their first postnatal visit to the 49 maternal and child health centres (MCHCs). Baseline characteristics including parental socio-economic position, birth characteristics, infant feeding, and second-hand smoke exposure were obtained using a self-administered questionnaire in Chinese. Passive follow-up via record linkage was instituted since 2005 to obtain: (1) weight and height from birth to age 5 years from the MCHCs; (2) weight and height, pubertal status, physiological well-being, and blood pressure from the Student Health Service; (3) hospital discharge records from the Hospital Authority; and (4) death records from the Death Registry. Surveys I and II concerning family history and psychological well-being, respectively, were implemented during 2008/9 and 2009/10. Survey III was sent to cohort families in 2011/12 with a measuring tape to collect self-measured waist and hip circumferences, weight, and height. In the end, 78% (n=5950) of the contactable cohort families responded to Survey III, from which 60% were telephone interviewed.

The study was approved by the University of Hong Kong-Hospital Authority Hong Kong West Cluster Joint Institutional Review Board and the Ethics Committee of the Department of Health, Government of the Hong Kong SAR, People's Republic of China.

Exposure

The main exposures were foetal and infant growth in terms of all 9 combinations of tertiles of birth weight for gestational age and infant growth. Birth weight for gestational age was calculated as the sex- and gestational age-specific birth weight z-score, relative to standards for contemporary Hong Kong Chinese infants interpolated onto a scale from 0.5 kg to 5.2 kg for each gestational week from 24 to 42 weeks using the Akima package in R. Infant growth was calculated as the change in weight z-score, ie standard deviation score, from birth to age 3 or 12 months. Weight z-score was calculated relative to the 2006 World Health Organization (WHO) growth

standards. We used the Akima package in R (version 2.3.1) to interpolate the WHO standards onto a daily scale, so that all weight z-scores were calculated at exact daily ages.

Outcome measures

The primary outcome measure was BMI and central adiposity at age 13 years. We used age- (in days) and sex-specific z-scores for BMI and height relative to the 2007 WHO growth standards. Central adiposity was proxied by waist circumference, z-scores for waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR). Waist and hip circumferences were reported by the participants. The waist circumference was measured at the narrowest part of the waist (at the umbilicus if unavailable) and the hip circumference was over the trochanters. A validity study of 172 randomly selected participants found a mean overestimation of 0.24 (95% confidence interval [CI], -0.84 to 0.37) cm on waist circumference and a mean underestimation of 0.85 (95% CI, 0.41 to 1.29) cm on hip circumference. The bias was not varied by weight status or parental education.

The secondary outcome measure was infection, proxied by the number of hospital admissions for respiratory infections or any infection during infancy, childhood, and adolescence. To check for any uncontrolled confounding by socio-economic position, we also considered admissions for accidents. Those without any record of hospital admission were assumed to have had no admission.

Statistical analysis

Multivariable linear regression was used to assess the association of foetal and infant growth with adiposity. Whether infant growth had different associations with adiposity by sex or birth weight for gestational age was assessed by comparing the Akaike information criterion (AIC) of models with and without the interaction terms. A smaller AIC indicates a better fitting model.

Potential confounders included sex, parity, obstetric conditions, early infant feeding practise, parental place of birth, parental education, parental BMI, and parental height. We additionally analysed the type of birth hospital and self-reported private hospital use on infections. We used multiple imputation for weight at ages 3 months (8.2% missing) and 12 months (10% missing). The results from ten imputed datasets were summarised into single estimates with CIs adjusted for missing data uncertainty.

Results

Participant characteristics

As of 30 April 2012, 8242 of 8327 participants were alive and had not withdrawn, of whom 7768 were term births. We further excluded 95 with birth defects and one with sex unknown, thus 7673 were analysed. Faster infant growth was more common among infants with lower birth weight for gestational age, shorter gestational age, or with more educated parents or being born in a private hospital (Table 1).

Infant growth and adiposity at age 13 years

At age 13 years, BMI of 6861 participants and waist and hip circumference of 5476 participants were measured. Waist circumference, WHR, and WHtR were positively related to BMI at age 13 years in both sexes, although this positive trend was less apparent in adolescents with a lower BMI (Fig). There was some evidence that the association of infant growth with adiposity at age 13 years differed by birth weight for gestational age and/or by sex. Table 1 shows that both foetal and infant growth at ages 0-3 months or 0-12 months were positively associated with BMI z-score and waist circumference at age 13 years after adjusting for place of birth, education, and body size of parents. The association of infant growth with BMI z-score was somewhat less among those born big. Those born big who grew fast in infancy had the greatest BMI and waist circumference at age 13 years. Foetal and infant growth were positively associated with WHtR among boys but not girls, but had little association with WHR. Results were unchanged when pubertal timing or height at age 13 years were included in the models.

Infant growth and hospital admission due to infection

A total of 3303 term births had at least one admission to a public hospital during 1-13.9 years. Admission was higher among boys, adolescents born lighter, and those born in public hospitals. The private hospital use due to infection after age 5 years was obtained from 50% of the cohort members, with 93% reporting no such admission. Growth rate was unrelated to admission due to respiratory infections, any infections, or accidents in infancy, childhood, or adolescence, after adjusting for confounders (Table 2). There was no interaction by sex or birth weight for gestational age.

Discussion

In the Children of 1997 birth cohort, faster foetal and infant growth were associated with greater BMI and greater waist circumference at age 13 years in both boys and girls. Nonetheless, foetal and infant growth had little association with WHR at age 13 years, and were only associated with WHtR among boys.

There are some limitations in this study. First, cohort members who were excluded due to missing adiposity information had relatively higher-educated parents. Nonetheless, the association of infant

TABLE 1. Changes in body mass index (BMI) z-score, waist circumference, waist-to-hip ratio (WHR) z-score, and waist-to-height ratio (WHtR) z-score at age 13 years for birth weight tertile groups by growth rate tertiles at ages 0-3 months and 0-12 months*

Growth rate tertile	Birth weight tertile (β [95% CI])					
	Boys			Girls		
	1st tertile	2nd tertile	3rd tertile	1st tertile	2nd tertile	3rd tertile
BMI z-score						
Age 0-3 months						
1st tertile	Ref	0.24 (0.02, 0.46)	0.48 (0.26, 0.69)	Ref	0.11 (-0.09, 0.31)	0.38 (0.20, 0.57)
2nd tertile	0.14 (-0.08, 0.36)	0.42 (0.20, 0.65)	0.61 (0.39, 0.83)	0.23 (0.03, 0.42)	0.34 (0.14, 0.53)	0.53 (0.33, 0.73)
3rd tertile	0.42 (0.21, 0.63)	0.69 (0.46, 0.91)	0.74 (0.49, 0.99)	0.33 (0.14, 0.52)	0.54 (0.34, 0.74)	0.61 (0.37, 0.85)
Age 0-12 months						
1st tertile	Ref	0.26 (0.04, 0.47)	0.45 (0.25, 0.65)	Ref	0.22 (0.00, 0.44)	0.47 (0.26, 0.67)
2nd tertile	0.19 (-0.02, 0.41)	0.47 (0.26, 0.68)	0.74 (0.51, 0.97)	0.29 (0.07, 0.51)	0.41 (0.20, 0.63)	0.69 (0.47, 0.91)
3rd tertile	0.44 (0.23, 0.64)	0.72 (0.50, 0.95)	0.84 (0.58, 1.10)	0.48 (0.27, 0.68)	0.66 (0.45, 0.88)	0.74 (0.49, 0.99)
Waist circumference (cm)						
Age 0-3 months						
1st tertile	Ref	1.95 (0.20, 3.69)	3.49 (1.79, 5.20)	Ref	0.10 (-1.53, 1.72)	1.92 (0.39, 3.45)
2nd tertile	1.03 (-0.76, 2.82)	3.21 (1.40, 5.03)	4.36 (2.58, 6.14)	0.25 (-1.36, 1.86)	1.60 (0.03, 3.17)	2.94 (1.30, 4.59)
3rd tertile	2.89 (1.20, 4.57)	5.47 (3.63, 7.31)	5.74 (3.63, 7.85)	1.35 (-0.16, 2.86)	2.05 (0.43, 3.68)	3.68 (1.72, 5.64)
Age 0-12 months						
1st tertile	Ref	1.61 (-0.10, 3.32)	3.06 (1.45, 4.67)	Ref	0.90 (-0.84, 2.64)	2.48 (0.87, 4.10)
2nd tertile	1.12 (-0.59, 2.84)	3.61 (1.91, 5.30)	5.58 (3.74, 7.41)	1.53 (-0.18, 3.24)	1.86 (0.21, 3.51)	4.06 (2.32, 5.79)
3rd tertile	3.02 (1.37, 4.68)	5.78 (3.97, 7.59)	6.29 (4.15, 8.42)	1.93 (0.31, 3.55)	3.22 (1.51, 4.92)	4.47 (2.48, 6.46)
WHR z-score						
Age 0-3 months						
1st tertile	Ref	0.05 (-0.14, 0.23)	0.04 (-0.14, 0.22)	Ref	-0.04 (-0.26, 0.18)	-0.02 (-0.22, 0.19)
2nd tertile	-0.04 (-0.23, 0.15)	0.01 (-0.18, 0.20)	0.10 (-0.10, 0.30)	-0.19 (-0.41, 0.03)	-0.07 (-0.28, 0.14)	-0.02 (-0.23, 0.21)
3rd tertile	0.07 (-0.11, 0.25)	0.10 (-0.09, 0.29)	0.07 (-0.15, 0.29)	-0.06 (-0.27, 0.14)	-0.04 (-0.26, 0.18)	0.07 (-0.18, 0.33)
Age 0-12 months						
1st tertile	Ref	0.00 (-0.19, 0.19)	0.07 (-0.11, 0.25)	Ref	0.05 (-0.18, 0.29)	-0.01 (-0.22, 0.21)
2nd tertile	0.03 (-0.16, 0.22)	0.04 (-0.14, 0.23)	0.09 (-0.11, 0.29)	-0.04 (-0.27, 0.19)	-0.04 (-0.26, 0.18)	0.09 (-0.14, 0.33)
3rd tertile	0.05 (-0.13, 0.22)	0.16 (-0.04, 0.36)	0.06 (-0.18, 0.30)	-0.08 (-0.30, 0.14)	-0.04 (-0.27, 0.19)	0.05 (-0.22, 0.31)
WHtR z-score						
Age 0-3 months						
1st tertile	Ref	0.12 (-0.07, 0.30)	0.20 (0.03, 0.38)	Ref	-0.10 (-0.31, 0.12)	0.08 (-0.12, 0.28)
2nd tertile	0.01 (-0.17, 0.20)	0.19 (0.00, 0.38)	0.21 (0.02, 0.40)	-0.06 (-0.27, 0.16)	0.04 (-0.16, 0.25)	0.10 (-0.12, 0.32)
3rd tertile	0.15 (-0.02, 0.33)	0.30 (0.11, 0.49)	0.31 (0.09, 0.52)	0.03 (-0.17, 0.23)	0.03 (-0.18, 0.25)	0.19 (-0.08, 0.45)
Age 0-12 months						
1st tertile	Ref	0.09 (-0.09, 0.27)	0.15 (-0.02, 0.32)	Ref	0.00 (-0.23, 0.23)	0.10 (-0.11, 0.31)
2nd tertile	-0.02 (-0.19, 0.17)	0.16 (-0.02, 0.34)	0.29 (0.10, 0.48)	0.07 (-0.16, 0.30)	0.00 (-0.22, 0.22)	0.20 (-0.03, 0.42)
3rd tertile	0.13 (-0.05, 0.30)	0.30 (0.11, 0.48)	0.23 (0.01, 0.45)	0.03 (-0.19, 0.24)	0.11 (-0.11, 0.34)	0.19 (-0.08, 0.45)

* Adjusted for gestational age, highest parental education, parental BMI, parental height, and parental place of birth

growth with adiposity did not differ by parental education. Second, the change in infant weight over time may be subjected to the regression to the mean, but this was avoided by using categorical exposure groups considering all possible combinations of infant growth and birth size. Third, self-measured waist and hip circumferences may incur error, but the validation study confirmed good agreement between self- and assessor-measured values.

In the same cohort, higher birth weight and

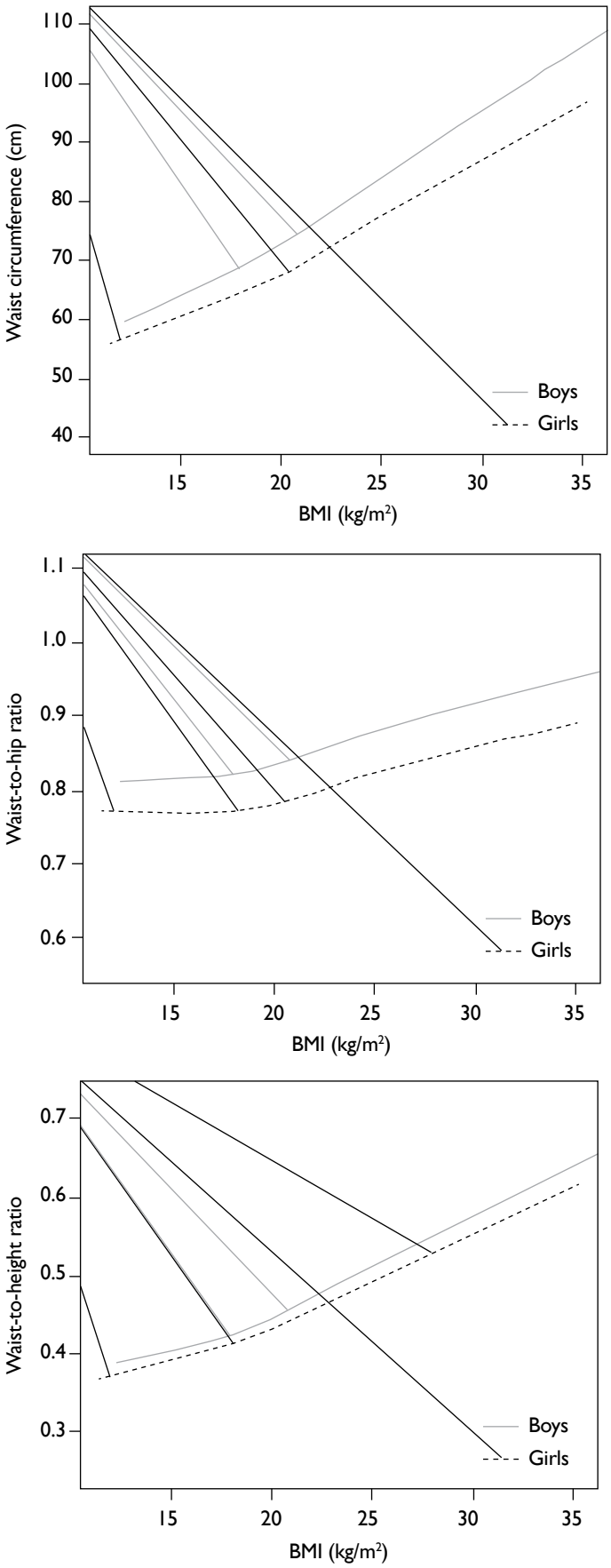

FIG. Waist circumference, waist-to-hip ratio, and waist-to-height ratio by body mass index (BMI) z-score at age 13 years

faster infant growth was associated with higher BMI at age 7 years,[1] with no immunological benefit.[3] At age 13 years, there was also no immunological benefit of infant growth, and faster foetal or infant growth was associated with greater BMI and waist circumference, which is consistent with another study.[4] Nonetheless, faster foetal or infant growth was not positively associated with central adiposity, as proxied by WHR in both sexes, or with WHtR among girls. There are several possible explanations for the differences in the associations of foetal and infant growth with measures of general and central obesity. First, foetal and/or infant growth may promote development of muscle mass, hence a higher BMI without substantially greater fat mass, as reflected by WHR. This possibility could not be examined further because of a lack of detailed measures of body composition for this cohort. Second, cohort members who grow faster in infancy have earlier pubertal onset and greater height,[5] hence higher BMI but possibly not higher WHR due to the redistribution of fat at puberty to more gynoid shapes among girls and android shapes among boys. Nonetheless, the associations were largely unchanged by additionally adjusting for pubertal status. Moreover, such a process might have been expected to generate different associations by sex, although it is possible that the influence of pubertal growth may not be fully expressed in boys who were at a relatively earlier stage of puberty than girls. Third, factors enabling faster growth during the mini-puberty of infancy could also enable a more intense puberty, and more pronounced pubertal development with differences by sex. We have previously suggested that up-regulation of the axis controlling growth over generations of improving living conditions would result in larger size, faster growth, and more sexually dimorphic body shapes,[2] including a more android body shape among men. In this case faster infant growth would be associated with higher levels of sex-steroids at puberty and more sexually dimorphic shapes at puberty. We do not currently have measures of pubertal sex-steroids for this cohort, so we cannot examine this possibility further.

Conclusion

Growing fast during infancy was positively associated with BMI and waist circumference, but not with WHR at age 13 years in both boys and girls or with WHtR among girls. Fast infant growth was not associated with any immunological benefits. Fast infant growth had different associations with different measures of adiposity. As such this may reflect differential sex-specific effects of infant growth, or its drivers, on different aspects of body composition, such as fat mass and muscle mass, or on body shape.

TABLE 2. Incident rate ratios (IRR) for hospital admissions due to respiratory infection, any infection, or accidents during infancy, childhood, and adolescence by growth rate tertiles at ages 0-3 months and 0-12 months*

Growth rate tertile	IRR (95% CI)		
	Respiratory infection	Any infection	Accident
Infancy			
Age 0-3 months			
1st tertile	1.00	1.00	1.00
2nd tertile	0.88 (0.70, 1.10)	0.86 (0.71, 1.03)	0.93 (0.57, 1.51)
3rd tertile	0.94 (0.74, 1.20)	0.94 (0.78, 1.14)	0.94 (0.56, 1.59)
Age 0-12 months			
1st tertile	1.00	1.00	1.00
2nd tertile	0.82 (0.65, 1.03)	0.90 (0.74, 1.08)	0.96 (0.56, 1.62)
3rd tertile	0.96 (0.75, 1.23)	1.01 (0.83, 1.22)	0.83 (0.48, 1.44)
Childhood			
Age 0-3 months			
1st tertile	1.00	1.00	1.00
2nd tertile	1.10 (0.93, 1.31)	0.99 (0.86, 1.14)	1.00 (0.76, 1.31)
3rd tertile	1.02 (0.84, 1.24)	1.00 (0.86, 1.16)	0.97 (0.73, 1.30)
Age 0-12 months			
1st tertile	1.00	1.00	1.00
2nd tertile	1.00 (0.84, 1.19)	0.93 (0.81, 1.07)	1.01 (0.77, 1.32)
3rd tertile	1.03 (0.85, 1.24)	0.98 (0.84, 1.14)	0.84 (0.62, 1.13)
Adolescence			
Age 0-3 months			
1st tertile	1.00	1.00	1.00
2nd tertile	0.89 (0.63, 1.25)	0.78 (0.59, 1.04)	1.41 (0.98, 2.02)
3rd tertile	0.97 (0.67, 1.40)	0.88 (0.65, 1.18)	1.20 (0.81, 1.78)
Age 0-12 months			
1st tertile	1.00	1.00	1.00
2nd tertile	0.81 (0.58, 1.15)	0.90 (0.74, 1.09)	1.31 (0.92, 1.88)
3rd tertile	0.85 (0.59, 1.22)	1.00 (0.82, 1.22)	1.28 (0.86, 1.91)

* Adjusted for birth weight for gestational age, gestational age, highest parental education, type of birth hospital, parental place of birth, and private hospital use since age 5 years due to infections

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Physical health needs, lifestyle choices, and quality of life among people with mental illness in the community

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KEY MESSAGES

1. People with severe mental illness (PSMI) demonstrated poor health profiles. Over two-thirds of the PSMI were overweight or obese. They scored significantly lower in all aspects of health-related quality of life, compared with the general population.
2. Few PSMI reported participation in preventive health behaviours such as testing blood cholesterol level, taking regular physical activity, receiving vaccinations, or undergoing cancer screening.
3. PSMI reported a moderate level of unmet needs across all domains. People with depression had a higher level of unmet needs than other diagnostic groups.
4. As predictors of life satisfaction for PSMI, depression and interpersonal problems were important factors for worse life satisfaction, whereas health-promoting behaviours, perceived social support, and self-esteem were important factors for better life satisfaction.
5. Applying the modified health belief model for PSMI, better physical and mental health-related quality of life and more-healthy lifestyle were associated with less barriers, higher responsiveness to cues to action, and higher health-specific self-efficacy.

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Introduction

According to the World Health Organization, health is a state of complete physical, psychological, and social well-being, rather than simply the absence of disease. Thus, to enhance the overall well-being of people with severe mental illness (PSMI), in addition to attending to their psychological and social needs, health needs assessment is essential.[1] Much attention has focused on the management of mental health but little on physical health needs. Such an imbalance neglects the interconnectedness between physical and mental health and the fact that PSMI may be at increased risk of physical health comorbidity.

The present study used the health belief model (HBM)[2] and health-specific self-efficacy[3] to examine the psychosocial determinants of health conditions and practices of PSMI. In some studies, health-specific self-efficacy is incorporated as a separate independent variable into the HBM. Findings of this study are important in the design of relevant community mental health services and health interventions that promote the quality of life (QoL) and the recovery of PSMI in Hong Kong.

Methods

This study was conducted from October 2009 to May 2011. A stratified sampling design was used to recruit PSMI from the Hong Kong community. Upon informed consent, PSMI were interviewed by a trained interviewer using structured questionnaires. On completion of the interview, participants were given a HK$70 supermarket coupon.

A total of 587 PSMI (55.0% female) with a mean age of 46.2 (standard deviation [SD], 10.8) years and a mean duration of mental illness of 17.7 (SD, 10.9) years were recruited. Most were diagnosed with schizophrenia spectrum disorders (70.2%), followed by major depression (14.3%), other mood disorders (8.0%), and others (7.5%). Of the participants, 68.8% had secondary education, 21.6% had primary education, 7.5% had post-secondary education, and 1.7% had no education. Characteristics of the sample and the community estimated by New Life Psychiatric Rehabilitation Association were comparable.

Self-report questionnaires included the Health Risk Factors Questionnaire (Chinese version), Health Promoting Practices Questionnaire, HBM Questionnaire, Health-specific Self-Efficacy Scale, Camberwell Assessment of Need Short Appraisal Schedule, Short Form Health Survey 12 Version 2 (SF-12v2), Life Satisfaction Scale, ENRICHD Social Support Instrument, Rosenberg Self-Esteem Scale, Behavior and Symptom Identification

Scale, and a medication side-effects list. Objective measures included height, weight, waist and hip circumferences, and blood pressure.

Results

Compared with the 2008-09 Hong Kong Chinese population mean,[4] our sample had significantly lower SF-12v2 scores across all physical and mental health domains (Table 1), and had heightened health risks in terms of body mass index, waist-to-hip ratio, and percentage with hypertension (Table 2). In the past year, only 23% reported having their cholesterol level tested, 19.8% reported having vaccinations, and <17% had cancer screening (half reported not knowing where to obtain cancer-related information). About 16.2% and 19.5% reported drinking and smoking habits, respectively. A larger proportion reported having regular exercise and adequate sleep.

The needs reported most by the PSMI were social needs (45%), followed by health needs (35%), daily function needs (35%), service needs (32%), and basic needs (29%) [Table 3]. The highest percentage of unmet needs was reported for intimate relationships, psychological distress, physical health, and psychotic symptoms, which were also among the areas of highest reported needs. Participants with depression (11.8%; SD, 12.71%) reported a significantly higher percentage of unmet needs than those with schizophrenia (7.5%; SD, 9.84%) or with other mood disorders (5.8%; SD, 8.3%), whereas participants with other mood disorders reported a significantly lower percentage of unmet needs than people with other mental illnesses (10.3%; SD, 15.98%).

To explain PSMI's life satisfaction, hierarchical regression analysis was conducted with sex, age, psychiatric diagnoses, medication side effects in block 1, psychiatric symptomatology in block 2, and health-promoting behaviours, social support, and self-esteem in block 3 as predictor variables. The overall model explained 53.4% of the total variance in life satisfaction ($F(15, 569)=45.54$, $P<0.001$). Being a male and older was positively related to life satisfaction. Among the psychiatric symptomatology, depression, interpersonal problems, and emotional lability were negatively related to life satisfaction. In addition, health-promoting behaviours, perceived social support, and self-esteem showed a significant positive relationship with life satisfaction. The overall model explained 14.4% of the total variance in unmet health needs ($F(14, 570)=8.02$, $P<0.001$), with lower impact of medication side effects and higher self-esteem being associated with lower percent of unmet health needs.

A path analysis was conducted to examine factors in the modified HBM integrating health-specific self-efficacy that explain healthy lifestyles and health-specific QoL, with covariates including age, psychiatric symptoms, medication side effects, perceived social support, and self-esteem accounted for in the model. Results indicated a satisfactory fit of the proposed model: $\chi^2=222.07$ (df =48, $P<0.01$); $\chi^2/df=4.63$; GFI=0.95; CFI=0.92; RMSEA=0.08 (90% CI, 0.07, 0.09). The modified HBM explained 29.7% variance of healthy lifestyles that in turn explained 13.3% and 33.5% variance of perceived physical and mental health status, respectively. The constructs of the modified HBM explained an additional 10.2% variance on healthy lifestyles (F Change (6, 573)=14.99, $P<0.001$). Lower levels of expected barriers, higher willingness to adopt a healthy lifestyle when faced with cues to action, and higher health-specific self-efficacy were associated with higher degrees of healthy lifestyles practice.

TABLE 1. Short Form Health Survey 12 Version 2 (SF-12v2) scores in people with severe mental illness (PSMI) versus the 2008-9 Hong Kong population mean

SF-12v2 subscale	Mean±SD score		T-test	P value
	PSMI	2008-9 population mean		
Physical functioning	68.1±29.0	87.3±22.4	-17.82	<0.001
Role physical	62.9±24.9	79.8±22.8	-15.99	<0.001
Bodily pain	60.9±29.9	77.6±25.0	-14.41	<0.001
General health	44.1±27.3	47.8±27.8	-3.28	<0.001
Vitality	50.7±27.1	62.4±25.4	-10.01	<0.001
Social functioning	65.4±28.3	81.8±23.8	-14.59	<0.001
Role emotional	65.7±25.9	77.2±21.5	-11.42	<0.001
Mental health	61.5±21.9	68.8±18.7	-8.51	<0.001

Discussion

PSMI demonstrated poor health profiles: 69.1% were overweight or obese and 18.6% were hypertensive. They scored significantly lower in all aspects of health-related QoL, compared with the general population. Although only a small number of PSMI reported smoking and drinking, few reported participation in preventive health behaviours: 23% reported having their cholesterol level tested, 19.8% reported having influenza vaccinations, and <17% ever had cancer screening. These findings are consistent with overseas studies that revealed that PSMI often engage in more health-compromising behaviours and less health-promoting behaviours, and are at heightened risk for coronary heart disease, diabetes, and other chronic physical illnesses.[5] It is important to raise the awareness of PSMI in health-promoting behaviours and preventive health practices.

Many PSMI, especially those with depression, lacked access to appropriate forms or adequate levels of care to deal with their recovery needs. Among the

TABLE 2. Health indices and preventive health practices of people with severe mental illness (PSMI)

Parameter	Mean±SD value or No. (%) of PSMI
Health indices	
Body mass index	25.57±4.77
Underweight (<18.5 kg/m2)	31 (5.3)
Normal (18.5-23 kg/m2)	150 (25.6)
At-risk overweight (23-26 kg/m2)	100 (17)
Obese (>26 kg/m2)	306 (52.1)
Waist-to-hip ratio	
Female (cut-off, 0.85)	0.88±0.07
Male (cut-off, 0.9)	0.92±0.07
Low risk	198 (33.7)
High risk	388 (66.1)
Blood pressure	
Systolic	122.80±17.08
Diastolic	77.19±10.88
Normal (<120 for systolic and <80 for diastolic)	262 (44.6) [24 on anti-hypertensive medication]
Prehypertension (120-140 for systolic and 80-90 for diastolic)	209 (35.6) [38 on anti-hypertensive medication]
Hypertension (>140 for systolic and >90 for diastolic)	109 (18.6) [38 on anti-hypertensive medication]
Preventive health practices	
In the past week	
Rigorous exercise	177 (30.2)
Days per week	3±2.16
<10 minutes each time	10 (5.75)
10-20 minutes each time	28 (15.9)
>20 minutes each time	138 (78.4)
Hours of sleep	7.77±1.95
Trouble sleeping/morning awakening	289 (49.2)
In the past month	
Drinking	95 (16.2)
Consumption	1.57±2.3 times, with 1.34±1.05 glasses each time
Smoking	114 (19.5)
Years of smoking	21.32±12.10
Daily consumption of cigarettes	14.84±9.68
In the past year	
Influenza vaccination	116 (19.8)
Cholesterol monitoring	135 (23)
Pap smear (females only)	50 (15.5)
Clinical breast exam (females only)	50 (15.5)
Mammogram (females only)	21 (6.5)
Ever in the lifetime	
Pneumonia vaccination	24 (4.1)
Hepatitis B vaccination	65 (11.1)
Prostate-specific antigen test and digital rectal examination (males only)	3 (1.1)
Faecal occult blood test (age >50 years only)	26 (11.3)
Flexible sigmoidoscopy (age >50 years only)	15 (6.5)
Colonoscopy (age >50 years only)	30 (13)

TABLE 3. Percentage of participants in 22 needs

Needs	% of participants (n=587)			
	No need	Need	Unclear	Unmet need
Basic needs	71	29	0	4
Accommodation	77	22	0	3
Food	69	31	0	4
Daytime activities	66	33	1	4
Health needs	64	35	1	8
Physical health	37	62	1	15
Psychotic symptoms	37	62	1	11
Psychological distress	47	53	1	17
Safety to self	67	32	1	6
Safety to others	74	25	1	3
Alcohol	94	6	0	0
Drugs	93	7	0	1
Social needs	54	45	1	14
Company	49	51	1	12
Intimate relationships	47	52	2	20
Sexual expression	66	31	2	11
Daily function needs	48	35	17	8
Looking after home	53	46	0	11
Self-care	63	37	0	5
Child care	20	14	66	4
Basic education	57	43	0	12
Service needs	67	32	1	7
Information about treatment and condition	51	46	3	12
Telephone	80	19	1	2
Transport	75	25	1	4
Money	53	47	0	14

various needs, social needs were the most likely to be unmet; service providers should pay attention to PSMI's interpersonal, intimacy, and sexual concerns. Evidence-based communication skills training should be offered to promote PSMI's social health, recovery, and reintegration into the community. Reducing medication side effects and boosting one's self-worth may also reduce the percentage of unmet needs.

Life satisfaction was negatively associated with having more symptoms in the depression and interpersonal problems, and positively associated with having social support and high levels of self-esteem, participating in health-promoting behaviours (such as adequate sleep, regular exercise, positive mindset, and relaxing activities). The modified HBM components were able to account for additional variance of healthy lifestyle even after controlling for covariates. Given healthy lifestyle was positively associated with physical and mental health-specific QoL, future research can target effective ways to facilitate positive health beliefs among PSMI, such as reducing expected barriers, increasing cues to action and health-specific self-efficacy.

This study had limitations. The target sample size of 700 could not be reached. A portion of potential participants might have dropped out because of their mental state or the length of the assessment. In addition, the study was cross-sectional in nature and causality could not be drawn. The use of self-reported questionnaires might have lowered the validity of the findings, as participants might have provided socially desirable responses.

Conclusion

By fostering their health beliefs and health-specific self-efficacy, service providers can potentially increase PSMI's health-promoting behaviours,

which are positively associated with their physical and mental health-related quality of life. To promote overall recovery and maximise the QoL of PSMI, service providers should increase PSMI's awareness of their health needs and encourage more health-promoting behaviours and preventive health care. Timely screening of health risks and associated interventions should be provided to PSMI. A full array of services should be provided to PSMI on the basis of needs. Service providers should regularly evaluate the effectiveness of community-based psychiatric rehabilitation services and delivery systems and provide stronger links between psychiatric services, psychosocial support, and physical health care. Service provision can then be streamlined to offer holistic health care and maximise potential for recovery in PSMI.

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Rapid eye movement sleep behaviour disorder and psychiatry: a case-control study

YK Wing *, SP Lam, JMY Tsoh, VCT Mok

KEY MESSAGES

1. Rapid eye movement sleep behaviour disorder (RBD) in psychiatric patients is associated with a high prevalence of sleep-related injuries to self (60%) and others (65%). Early medical attention and intervention are indicated.
2. The aetiology of RBD in psychiatric patients is not simply a drug-induced condition, but involves a combination of clinical factors that include mood and sleep symptoms and psychotropic medications.
3. RBD in older persons is a precursor to neurodegenerative disorders. Olfactory dysfunction seen in the relatively young psychiatric patients may be a subtle sign of an early neurodegenerative process.
4. The aetiology of an underlying neurodegenerative process in psychiatric RBD patients should be further investigated.

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Introduction

Over the past two decades, a novel parasomnia—rapid eye movement (REM) sleep behaviour disorder (RBD)—has been recognised. It is characterised by a loss of normal REM-sleep-related muscle atonia. Sufferers may therefore 'act out' their dreams, usually of a violent nature, with consequent sleep-related injury (SRI) to themselves and bed-partners.[1,2]

The prevalence of typical RBD is 0.38% with an elderly male predominance. RBD is regarded as a precursor to synucleinopathy-related neurodegenerative diseases (such as Parkinson's disease and Lewy body dementia).[1] Approximately 26 to 92% of typical RBD sufferers will go on to develop a neurodegenerative disease. Early neurocognitive markers (eg olfactory dysfunction) have been identified in RBD patients who do not yet exhibit clinical signs of a neurodegenerative disease.

There have been increasing reports of RBD features in psychiatric patients. These patients were younger and mostly female, compared with typical RBD patients. A clinical epidemiological survey of psychiatric patients revealed that lifetime and 1-year prevalence of RBD symptoms was 5.8% and 3.8%, respectively, which was ten times more common than in typical RBD patients.[3] The condition was associated with prescription of the newer types of antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs).[3,4] One out of 20 patients prescribed a SSRI develop RBD in their lifetime.[3] The pathophysiological mechanism on how SSRIs, mental state, and individual vulnerabilities interact and culminate in attacks of RBD is unclear. It is unclear whether it is a spectrum or variant of typical RBD. Not all patients prescribed an SSRI develop the condition. It has been suggested that SSRIs are associated with loss of REM muscle atonia in asymptomatic patients. This study aimed to determine the clinical risk factors and the presence of early neurocognitive deficits in psychiatric patients with RBD.

Methods

This case-control study was conducted from October 2009 to September 2011. According to the International Classification of Sleep Disorder II criteria, 40 consecutive RBD patients were identified in a psychiatric clinic. They were matched with two control arms: (1) sex- and age-matched healthy controls from the community, and (2) sex-, age-, and diagnosis-matched psychiatric controls from the psychiatric clinic.

All subjects underwent structured clinical interview by trained interviewers for sleep and psychiatric diagnoses and questionnaires on sleep and mood symptoms, using the RBD questionnaire-Hong Kong (RBDQ-HK),[5] Beck Depression Inventory (BDI), and Hospital Anxiety and Depression Scale (HADS), as well as neurocognitive assessment including olfaction identification test, Chinese version of the mini-mental state examination (MMSE), and Mattis dementia rating scale.

All subjects also underwent one overnight video-polysomnographic study to measure the degree of loss of REM muscle atonia by REM-related EMG activities (REMREEA).[6]

Results

The three groups were comparable in terms of demographics. The two psychiatric groups were comparable in terms of psychiatric diagnosis and antidepressant usage (Table 1). However, co-morbid post-traumatic stress disorder (PTSD) was noted in seven RBD patients and one psychiatric controls. Psychiatric patients with RBD were also more likely to be prescribed benzodiazepines (including clonazepam), which are commonly prescribed for RBD. They also had the highest BDI and HADS scores, and more insomnia and recurrent nightmares.

Among psychiatric patients with RBD, 60% reported a history of SRI to self, 65% reported a history of attempted assault on bed-partner during their dream enactment, and 52.5% reported a history of falling out of bed during sleep. Most SRIs were mild (bruises or abrasions), but 12.5% were more severe (head injuries or lacerations).

The three groups were comparable in terms of sleep architecture (sleep efficiency, wake-after-sleep-onset, and REM density). However, healthy controls had shorter sleep latency and REM latency, longer slow-wave sleep, and lower apnoea-hypnoea index than the other groups (Table 2). Psychiatric patients with RBD had significantly higher total, tonic, and phasic scores in REMREEA, which is the pathognomonic sign of RBD. The REMREEA was associated with BDI and HADS scores (mood symptoms) and use of antidepressants (Table 3). Compared with phasic EMG activity, tonic EMG activity was associated with nightmare and prescription of benzodiazepines.

Overall, the healthy controls showed better neurocognitive performance than the other two groups in terms of olfactory identification test, MMSE, and the Mattis dementia rating scale (Table 3). Although psychiatric patients with RBD and psychiatric controls had comparable neurocognitive scores, there was a dosing relationship in olfaction identification test across psychiatric patients with RBD, psychiatric controls, and healthy controls (linear-by-linear association, P=0.002).

Discussion

In addition to its association with antidepressant usage, RBD in psychiatric patients was also associated with mood and sleep symptoms, and possibly early neurocognitive deficit. RBD results in SRI to self and bed-partners, and thus early attention, management, and exploration of the underlying pathophysiology is warranted. Although most believed that RBD was a drug-induced condition among patients taking antidepressants, in this study we found that the case and control groups differed significantly in mood and sleep symptoms, albeit comparable diagnoses and psychotropic prescriptions. The psychiatric patients with RBD had more anxiety and depressive symptoms, insomnia, and nightmares, all of which are associated with anxiety and mood disturbances. In addition, nightmare is a core symptom of RBD. Although most studies emphasise the importance of loss of REM-related muscle atonia as the pathophysiology of RBD, we suggest that nightmare also serves as a supratentorial drive to precipitate dream enactment features of RBD in susceptible subjects. Co-morbid PTSD in psychiatric patients with RBD is a common condition of RBD after exclusion of potential psychotropic effects. Although the exact pathological mechanism is not identified, it has been suggested that in PTSD, the decrease in the number of Locus Ceruleus neurons may account for both PTSD and RBD symptoms. We propose that RBD in psychiatric patients has a complex aetiology with several clinical factors (including mood and sleep symptoms) that increase the risk of developing RBD symptoms when taking psychotropic medications, particularly antidepressants. Simply considering RBD as a condition secondary to psychotropics use may be misleading, and may hinder further investigation and management of other contributory factors.

The severity of loss of REM-related muscle atonia was quantified by the REMREEA score. In normal physiology, REM sleep is associated with muscle atonia. Patients with RBD symptoms had a much higher REMREEA including both phasic and tonic activities. The increase in REMREEA in both psychiatric RBD patients and psychiatric controls compared with healthy controls may be in part due to the use of antidepressants that increase REM muscle activity during REM sleep. Nonetheless, psychiatric RBD patients still had significantly higher REMREEA than psychiatric controls. Benzodiazepines, particularly clonazepam, also affect phasic EMG activity. Future studies to investigate the effect of benzodiazepines and their dosage and length of use in psychiatric RBD patients are needed in order to determine their effect on the REMREEA. The presence of tonic REMREEA was noted in psychiatric RBD patients only. Long-lasting REM muscle activity (tonic activity), rather than short-lasting one (phasic activity), was independently associated with a reduction in striatal dopamine transporters, which is regarded as the pathophysiology of RBD. Our study further supports tonic activity as a hallmark feature of RBD.

Neurodegeneration is an important pathophysiological mechanism in typical RBD in the elderly population.[2] Early neurocognitive and neurobiological markers have been reported in

TABLE 1. Comparison of clinical characteristics in psychiatric patients with rapid eye movement sleep behaviour disorder (RBD), psychiatric controls, and healthy controls*

Clinical characteristics	Mean±SD or No. (%) of subjects			P value*			
	Psychiatric patients with RBD (group 1) [n=40]	Psychiatric controls (group 2) [n=40]	Healthy controls (group 3) [n=40]	1 vs 2 vs 3	1 vs 2	2 vs 3	1 vs 3
Age (years)	46.9±9.3	47.7±10.8	46.9±4.0	NS	NS	NS	NS
Male	12 (30)	10 (25)	12 (30)	NS	NS	NS	NS
Body mass index (kg/m^2)	24.3±3.3	25.2±4.5	23.8±2.5	NS	NS	NS	NS
Smoking	11 (33.3)	4 (19.0)	3 (18.8)	NS	NS	NS	NS
Education level				NS	NS	<0.05	<0.05
Primary level or below	9 (22.5)	8 (20)	1 (2.5)				
Secondary level	22 (55)	24 (60)	29 (72.5)				
Tertiary level or above	9 (22.5)	8 (20)	10 (25)				
Psychiatric diagnoses (life time)	40 (100)	40 (100)	0	<0.01	NS	<0.01	<0.01
Major depressive disorder	36 (90)	38 (95)	0	-	NS	<0.01	<0.01
Bipolar affective disorder	3 (7.5)	1 (2.5)	0	-	NS	NS	NS
Anxiety disorder	1 (2.5)	1 (2.5)	0	-	NS	NS	NS
Co-morbid post-traumatic stress disorder	7 (18.4)	1 (2.5)	0	-	<0.05	NS	<0.01
Use of psychotropics	37 (92.5)	35 (87.5)	0	<0.01	NS	<0.01	<0.01
Antidepressants	33 (82.5)	33 (82.5)	0	-	NS	<0.01	<0.01
Selective serotonin reuptake inhibitor	25 (62.5)	21 (52.5)	0	-	NS	-	-
Serotonin-norepinephrine reuptake inhibitor	7 (17.5)	5 (12.5)	0	-	NS	-	-
Noradrenaline and selective serotonin antidepressants	0	3 (7.5)	0	-	NS	-	-
Tricyclics	1 (2.5)	7 (17.5)	0	-	NS	-	-
Benzodiazepine	21 (52.5)	4 (10)	0	-	<0.01	NS	<0.01
Clonazepam	13 (32.5)	2 (5.0)	0	-	<0.01	NS	<0.01
Non-benzodiazepine hypnotics	5 (12.5)	9 (22.5)	0	-	NS	<0.01	NS
Antipsychotics	11 (27.5)	8 (20)	0	-	NS	<0.01	<0.01
Mood stabiliser	4 (10.0)	3 (7.5)	0	-	NS	NS	NS
Polypharmacy (≥2 types)	29 (72.5)	28 (70)	0	-	NS	<0.01	<0.01
Beck Depression Inventory†	13.9±8.6	7.6±6.3	2.1±2.4	<0.01	<0.01	<0.01	<0.01
Hospital Anxiety and Depression Scale†	19.4±4.5	17.9±3.6	15.3±2.5	<0.01	NS	<0.01	<0.01
Anxiety subscale	8.9±2.5	8.8±2.5	7.1±1.8	<0.01	<0.05	<0.01	<0.01
Depression subscale	9.1±2.6	9.0±1.8	8.2±1.6	<0.05	NS	<0.05	<0.05
RBD questionnaire-Hong Kong†	45.1±14.7	7.6±5.3	6.0±5.2	<0.01	<0.01	NS	<0.01
Factor 1 dreams related	18.6±5.4	6.1±5.2	5.2±4.5	<0.01	<0.01	NS	<0.01
Factor 2 behavioural	26.5±10.9	1.5±2.2	0.8±1.7	<0.01	<0.01	NS	<0.01
Insomnia >3/week	11 (27.5)	8 (20)	1 (2.5)	<0.01	NS	<0.05	<0.01
Habitual snoring >3/week	0	0	0	-	-	-	-
Nightmares >1/week	19 (47.5)	2 (5.0)	1 (2.5)	<0.01	<0.01	NS	<0.01
Sleep-related hallucination >1/month	5 (12.5)	0	0	<0.01	NS	-	NS
Sleep paralysis >1/month	4 (10.0)	0	0	<0.05	NS	-	NS

* NS denotes not significant

† Kruskal-Wallis test (1 vs 2 vs 3) and Mann-Whitney *U* test (1 vs 2, 2 vs 3, and 1 vs 3)

TABLE 2. Comparison of polysomnographic data in psychiatric patients with rapid eye movement sleep behaviour disorder (RBD), psychiatric controls, and healthy controls

Polysomnographic data	Mean±SD			P value*			
	Psychiatric patients with RBD (group 1) [n=40]	Psychiatric controls (group 2) [n=40]	Healthy controls (group 3) [n=40]	1 vs 2 vs 3	1 vs 2	2 vs 3	1 vs 3
Sleep efficiency (%)	82.3±8.4	82.2±8.0	83.0±8.8	NS	NS	NS	NS
Wake after sleep onset (minutes)	63.0±37.5	68.1±34.6	64.2±33.2	NS	NS	NS	NS
Sleep latency (minutes)	22.1±18.7	17.2±12.2	14.5±12.1	NS	NS	NS	NS
REM sleep latency (minutes)	156.7±90.4	177.1±94.0	111.1±43.3	<0.01	NS	<0.01	NS
Stage 1 sleep (%)	48.6±26.4	37.9±21.1	29.3±15.5	<0.01	NS	NS	<0.01
Stage 2 sleep (%)	244.1±82.8	220.8±93.4	214.4±96.3	NS	NS	NS	NS
Slow wave sleep (%)	14.9±42.0	20.0±30.8	29.0±48.2	<0.01	<0.01	NS	<0.01
REM sleep (%)	78.2±37.3	91.5±56.3	88.7±19.7	NS	NS	NS	NS
REM density (%)	19.6±11.2	22.6±11.9	18.7±6.5	NS	NS	NS	NS
Apnoea-hypnoea index	11.0±13.9	10.3±12.0	6.5±7.8	NS	NS	NS	NS
Periodic leg movement index	8.5±15.3	9.4±16.3	4.9±12.5	NS	NS	NS	NS
REM-related EMG activity, chin (%)							
Total	16.0±18.1	5.6±4.7	3.5±2.9	<0.01	<0.01	NS	<0.01
Tonic	3.2±7.8	0±0	0±0	<0.01	<0.01	NS	<0.01
Phasic	12.6±15.9	5.6±4.7	3.5±2.9	<0.01	<0.01	NS	<0.01

* Kruskal-Wallis test (1 vs 2 vs 3), Mann-Whitney *U* test (1 vs 2, 2 vs 3, and 1 vs 3), and NS denotes not significant

TABLE 3. Comparison of neurocognitive data in psychiatric patients with rapid eye movement sleep behaviour disorder (RBD), psychiatric controls, and healthy controls

Neurocognitive data	Mean±SD			P value*			
	Psychiatric patients with RBD (group 1) [n=40]	Psychiatric controls (group 2) [n=38]	Healthy controls (group 3) [n=40]	1 vs 2 vs 3	1 vs 2	2 vs 3	1 vs 3
Mini-mental state examination	28.6±1.3	28.6±1.6	29.3±0.8	NS	NS	NS	NS
Alcohol sniff test	22.0±7.8	20.6±9.5	21.3±8.3	NS	NS	NS	NS
Olfactory identification test ≥4 items (%)	28 (70)	30 (78.9)	38 (95)	<0.01†	NS	NS	<0.01
Mattis dementia rating scale							
Total	138.6±5.5	138.9±5.2	141.6±2.0	NS	NS	NS	<0.05
Attention	36.4±0.8	36.4±0.8	36.9±0.4	<0.01	NS	<0.01	<0.01
Initiation	36.3±1.9	36.2±1.7	36.8±0.7	NS	NS	NS	NS
Construction	5.7±0.8	5.7±0.6	6.0±0.2	NS	NS	NS	NS
Conceptualisation	36.4±2.9	36.6±2.8	38.1±1.3	<0.01	NS	NS	<0.01
Memory	23.9±1.6	23.9±2.8	24.0±1.4	NS	NS	NS	NS

* Kruskal-Wallis test (1 vs 2 vs 3), Mann-Whitney *U* test (1 vs 2, 2 vs 3, and 1 vs 3), and NS denotes not significant
† Liner-by-liner association

idiopathic RBD, such as olfactory dysfunction and executive function abnormalities. In our study, these clinical tests were negative. A dosing effect was observed among the three groups in olfactory dysfunction, at which RBD patients had the poorest performance, but the difference was not significant between psychiatric RBD patients and psychiatric controls. These negative findings may suggest that neurodegeneration is not the underlying pathophysiology, or that our subjects were too young to develop prominent neurodegeneration. Our RBD patients were much younger than the older typical RBD patients (mean age, 46 vs 62 years). Among all early neurodegenerative markers documented in

RBD of an older population, olfactory dysfunction is a sensitive predictor that is measureable at least 5 years before the onset of clinical neurodegeneration with a slow progression at the preclinical stage.[7] The dosing effect in olfactory function may suggest a subtle deficit, and further studies are needed. In both RBD and Parkinson's disease, depression is a risk factor for neurodegeneration. Depression or its certain subtype may predispose individuals to the development of RBD, and the presence of mood and sleep symptoms as well as the use of antidepressants may trigger RBD symptoms in susceptible psychiatric patients. Further longitudinal follow-up is warranted to monitor the progress and course of any neurodegenerative outcome among psychiatric RBD patients.

Conclusion

The aetiology of RBD in psychiatric patients is not only drug-induced, but involves both mood and sleep symptoms. There may be early neurodegenerative components; further longitudinal follow-up of a psychiatric RBD cohort to identify any neurodegeneration is needed.

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Infant or childhood obesity and adolescent depression

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KEY MESSAGES

1. Higher body mass index was not associated with depressive symptoms in early adolescence.
2. Depressive symptoms were associated with several unhealthy behaviours (ever-smoking, ever-drinking, and unhealthy diet). Higher Rutter score was associated with ever-smoking.

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Introduction

Depression is a leading cause of morbidity. The prevalence of common mental disorders has been reported to be 16.4% in a small but representative population of Hong Kong Chinese adolescents.[1] Most psychiatric disorders in adults are thought to originate in childhood and adolescence. There may be risk factors for developing unhealthy behaviours, with life-long detrimental effects on health. The pathway to depression and obesity may be similar.[2] In the west, both depression and obesity tend to be associated with lower socio-economic status. In Hong Kong, there is little social patterning of early life obesity.[3] This study used a large, population-representative Hong Kong Chinese birth cohort 'Children of 1997' to examine longitudinally the association of birth weight and life course body mass index with psychological well-being in late childhood and with depressive symptoms in early adolescence. The association of psychological well-being with adolescent health behaviours was also examined.

Methods

This study was conducted from October 2009 to January 2013. It was approved by the University of Hong Kong-Hospital Authority Hong Kong West Cluster Joint Institutional Review Board. The Children of 1997 birth cohort has been described elsewhere.[3] In brief, it is a population representative birth cohort consisting of 88% of children born in April to May in 1997 in Hong Kong. Height/length and weight measurements at 3 months, 9 months, 36 months were collected from the Maternal and Child Health Centres. The health checks at the Student Health Service included measurement of height and weight every year from age 6 years and assessment of pubertal status and some aspects of psychological well-being in alternate years. In 2010-2012, a questionnaire was used to obtain depressive symptoms, environmental stressors, and health behaviours of the cohort from age 12 to 15 years and their families.

Birth weight was considered as sex- and gestational age-specific z-scores. Adiposity was proxied by body mass index (BMI) z-score in infancy (3 months and 9 months), childhood (~3 years, ~7 years, ~9 years and ~11 years) and adolescence (~12 years) for depressive symptoms only, relative to the 2006 and 2007 World Health Organization growth references. Childhood overweight (or obesity) was defined as a BMI for age and sex equivalent to an adult BMI of ≥25.

Psychological well-being was evaluated using the Chinese version of the Revised Parent's Rutter Scales[4] for emotional and behavioural outcomes (higher scores indicate worse outcome), the Chinese version of the Form A of the Culture-Free Self-Esteem Inventories[5] for self-esteem (lower scores indicate lower self-esteem), and the Patient Health Questionnaire (PHQ)-9[6] for depressive symptoms (higher scores indicate depression). Smoking and drinking was considered as never and ever. Diet was assessed from a food frequency questionnaire and dichotomised as a healthy or unhealthy diet.[7] Physical activity was counted as hours of physical activity per day and dichotomised as low (<1 hour per day) or high (1+ hour per day).

Multivariable linear regression was used to assess the adjusted association of birth weight and life-course BMI with psychological well-being. Multivariable logistic regression was used to assess the adjusted association of psychological well-being with health behaviours. Whether association differed by sex from the heterogeneity across strata and the significance of the relevant interaction terms was assessed. Multiple imputation was used for missing exposures and confounders.

Results

From the Student Health Service, Rutter scores of 5589 children and self-esteem scores of 7089 children at ~11 years were available. Valid responses were obtained for depressive symptoms (n=5799), ever-smoking (n=5798), ever-drinking alcohol (n=5794), physical activity (n=3688), and diet (n=3657).

The mean Rutter score at ~11 years was 8.4 (standard deviation [SD], 6.0). The mean self-esteem score at ~11 years was 36.6 (SD, 7.4). The mean PHQ-9 score at ~13 years was 3.1 (SD, 3.5). Higher maternal depressive symptoms, feeling overwhelmed by school work, and poor perceived academic performance were all independently associated with higher Rutter score, lower self-esteem, and more depressive symptoms.

After adjusting for age, sex, and socio-economic status, lower birth weight was associated with a higher Rutter score at ~11 years, but BMI from infancy to childhood was not associated with Rutter score (Table 1). Birth weight was not associated with self-esteem at ~11 years, but a higher BMI at 7, 9, and 11 years was associated with lower self-esteem. Birth weight and BMI from infancy to age ~12 years was not associated with depressive symptoms at ~13 years. Similar results were obtained for depressive symptoms using multivariable partial least squares

TABLE 1. Adjusted association of birth weight and body mass index z-scores at different ages with Rutter score and self-esteem score at ~11 years and with Patient Health Questionnaire (PHQ)-9 score for depressive symptoms at ~13 years*

Variable	Rutter score	Self-esteem score	PHQ-9 score
	β (95% CI)	β (95% CI)	β (95% CI)
Birth weight	-0.04 (-0.18, 0.10)	-0.24 (-0.40, -0.08)	0.08 (-0.12, 0.27)
Age			
3 months	-0.09 (-0.30, 0.11)	0.005 (-0.21, 0.21)	-0.05 (-0.29, 0.20)
9 months	0.08 (-0.15, 0.32)	-0.05 (-0.32, 0.22)	-0.03 (-0.43, 0.38)
3 years	0.04 (-0.24, 0.32)	-0.20 (-0.38, -0.03)	-0.12 (-0.47, 0.23)
7 years	-0.10 (-0.44, 0.23)	-0.17 (-0.30, -0.04)	-0.20 (-0.35, -0.04)
9 years	-0.02 (-0.36, 0.32)	-0.14 (-0.26, -0.02)	-0.21 (-0.35, -0.06)
11 years	0.17 (-0.34, 0.68)	-0.10 (-0.22, 0.02)	-0.25 (-0.39, -0.10)
12 years	-0.03 (-0.47, 0.41)	-	-

* Adjusted for age, sex, parental education, mother's place of birth, and survey mode for PHQ-9

TABLE 2. Adjusted association of Rutter score, self-esteem score, and Patient Health Questionnaire (PHQ)-9 score with ever smoking, ever drinking, low physical activity, and unhealthy diet

Model*	Rutter score >12	Self-esteem score ≤19	PHQ-9 score ≥11
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Ever-smoking (90/5893, 1.5%)			
1	1.11 (1.05, 1.18)	0.95 (0.91, 0.99)	1.15 (1.09, 1.22)
2	1.09 (1.02, 1.16)	0.97 (0.92, 1.03)	1.14 (1.04, 1.24)
Ever-drinking (545/5887, 9.3%)			
1	1.02 (0.99, 1.05)	0.97 (0.95, 0.98)	1.11 (1.08, 1.14)
2	1.00 (0.98, 1.03)	0.98 (0.96, 1.00)	1.11 (1.07, 1.16)
Low physical activity (2483/3738, 66.4%)			
1	1.01 (1.00, 1.03)	0.98 (0.97, 0.99)	1.02 (1.00, 1.04)
2	1.00 (0.99, 1.02)	0.98 (0.97, 0.99)	1.01 (0.99, 1.03)
Unhealthy diet (599/3925, 15.3%)			
1	1.02 (1.00, 1.04)	0.97 (0.95, 0.98)	1.06 (1.03, 1.08)
2	1.00 (0.98, 1.02)	0.97 (0.96, 0.99)	1.04 (1.01, 1.07)

* Model 1 adjusted for age, sex, socio-economic status, parental marital status and survey mode, whereas model 2 additionally adjusted for the other measures of psychological well-being

regression to take account of measurements potentially being collinear. There was no evidence of different associations by sex (all p-values for interactions >0.05).

A high level of depressive symptoms was more common among adolescents without two parents living at home, and among adolescents whose parents had depressive symptoms. A minority of adolescents reported ever smoking (1.5%) or ever use of alcohol (9.3%), 15% had an unhealthy diet and 66% reported low physical activity. After adjusting for age, sex, socio-economic status, parental marital status, survey mode, and the other two measures of psychological well-being, a higher Rutter score was independently associated with ever-smoking, whereas lower self-esteem was independently associated with low physical activity and unhealthy diet, and more depressive symptoms were independently associated with ever smoking, ever use of alcohol and unhealthy diet (Table 2). There was little evidence that the associations differed by sex (P>0.05 for interaction).

Discussion

In the Children of 1997 birth cohort, birth weight and life-course BMI had a limited domain-specific association with psychological well-being. There was little evidence that birth weight or life-course BMI was associated with early adolescent depressive symptoms. Nonetheless, lower birth weight was associated with higher Rutter score at ~11 years, and higher BMI in late childhood was associated with lower self-esteem at ~11 years. Similarly, there was a domain-specific association of psychological well-being with health behaviour. Depressive symptoms were associated with unhealthy behaviours (ever-smoking, ever-drinking, and unhealthy diet), although higher Rutter score was associated with ever-smoking, and lower self-esteem was associated with low physical activity and unhealthy diet.

There were limitations to the study. Psychological well-being based on the questionnaire scores is not the same as a diagnosis. In addition, depressive symptoms were assessed at the same time as health behaviours.

Prevention of low birth weight and obesity among children is important. Poor psychological well-being in adolescence may be a forerunner of life-long unhealthy behaviour, with implications for prevention, if our findings are replicated in an evaluation of an intervention or a Mendelian randomisation study.

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Caries risk assessment programmes for Hong Kong children

XL Gao *, ECM Lo, CH Chu, SCY Hsu

KEY MESSAGES

1. Several caries risk factors/indicators were identified and serve as important references for targeted education and intervention in Hong Kong children.
2. A caries risk assessment programme outperformed other programmes and is epidemiologically and clinically useful for identifying caries-susceptible children.
3. The findings of this study will contribute to cost-effective caries prevention/intervention and optimised treatment planning.

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Introduction

The prevalence of dental caries (tooth decay) in early childhood is high. Early childhood caries (ECC) is associated with caries in permanent dentition and lethal systemic infections. In many developed countries, 25% of children bear 75-80% of caries lesions. Caries prevention should be targeted at high-risk individuals. Identifying high-risk pre-schoolers through caries risk assessment (CRA) is of great importance for caries control and cost control. The CRA should also be an integral part of diagnosis and treatment planning to optimise clinical outcomes.

Several CRA programmes have been developed for pre-schoolers, including the Caries-risk Assessment Tool (CAT),[1] the Caries Management by Risk Assessment (CAMBRA),[2] the Cariogram,[3] and the NUS-CRA biopsychosocial models.[4] This study aimed to compare the accuracy of various CRA programmes in predicting the caries risk among Hong Kong pre-schoolers.

Methods

This study was conducted from October 2009 to March 2012. Ethical approval was obtained from the Institutional Review Board of the University of Hong Kong / Hospital Authority Hong Kong West Cluster (#UW 08-400). Parental written consent was obtained for all grade-1 participants (3 years of age) from four kindergartens.

At baseline, each child and his/her parent/guardian were required to complete a questionnaire, an oral examination, and a biological test. The questionnaire was completed by the child's parents to collect information about the child's socio-demographic background, oral health behaviour (diet, oral hygiene habits, use of topical fluorides, and utilisation of dental services), and systemic condition, as well as parental knowledge of and attitude toward oral health. The oral examination was performed by a trained and calibrated examiner. Examination was repeated in 10% of subjects to assess intra-examiner reliability. The tooth status was mainly assessed by visual inspection, aided by tactile inspection if necessary. No radiographs were taken. The World Health Organization diagnostic criteria and procedures were followed and caries was recorded at the cavitation level. White-spot lesions—a risk indicator in the CAT and CAMBRA programmes—were also recorded. Oral hygiene status was evaluated using the Silness-Löe Plaque Index. Any developmental defect (eg hypoplasia) or dental appliance was recorded. The biological test assessed the stimulated saliva flow rate, buffering capacity, and levels of *mutan Streptococci* and *Lactobacilus*. Standard laboratory procedures were followed for the incubation of bacteria, acquirement of readings, and disposal of biological waste.

Children's caries risk was assessed using the various CRA programmes (CAT, CAMBRA, Cariogram, and NUS-CRA). For the CAT and CAMBRA, children were classified into 3 risk groups based on risk factors/indicators. For the Cariogram and NUS-CRA, caries risk was calculated using algorithms and expressed as % chance of caries in 1 year. In addition, both comprehensive and screening programmes were used, with and without biological tests. Rating criteria stipulated in the user instructions of each programme were followed.

The tooth status of each child was reviewed after 6, 12, and 18 months. The change in number

of decayed, missing, or filled teeth (Δdmft) was calculated as the disease outcome. The information on dental care received by the child during the follow-up period was also collected. When Δdmft was ≥0, risk factors/indicators were identified through multiple logistic regression. The performance of the CRA programmes was compared using receiver operating characteristics (ROC) analysis, by comparing the predicted risk with the short-term (6-month), medium-term (12-month) and long-term (18-month) caries incidence (Δdmft ≥0) [dichotomous]. The performance measures included sensitivity, specificity, accuracy, positive and negative predictive values, and area under ROC curve (AUC).

Results

Of 585 eligible children, 560 participated (response rate, 96%). At baseline, 544 participants (282 boys and 262 girls) were examined. After 6, 12, and 18 months, 508 (93%), 485 (89%), and 462 (85%) of participants were followed up. The intra-examiner reliability was high (Kappa=0.964). Those who completed the study and those who were lost to follow-up were comparable in terms of socio-demographic background and baseline caries experience, except that more girls than boys did not complete the study (P<0.05).

Within 12 months, 178 (36.7%) children developed new caries (Δdmft >0). The mean±standard deviation increment in dmft was 0.78±1.36. Several caries risk factors were identified, including father's education level, prolonged breastfeeding, bedtime feeding, sweet intake, toothbrushing frequency, residential history in a non-fluoridated community, plaque amount, past caries, and levels of *mutan Streptococci* and *Lactobacilus* (P<0.05).

Table 1 shows the caries increment among children classified in different risk groups by different study programmes. In the CAT and CAMBRA, most children were defined as high risk; only a small proportion was defined as moderate risk. Under the CAT, no participant was rated as low risk. In contrast, under the Cariogram and NUS-CRA, most children were defined as very low or low risk. Overall, there was a gradient in caries increment from lower to higher risk groups under all programmes. Nevertheless, no significant difference in caries increment was noted between some of the risk groups.

Table 2 shows the positive and negative predictive values of the CRA programmes. For CAMBRA, both possible cut-off points (≥moderate risk and ≥high risk) were explored. With CAT, no child was considered as low risk, and thus ≥moderate risk was no more a valid cut-off point, and only the ≥high risk cut-off point was used. For Cariogram and NUS-CRA, the best cut-off points identified by the ROC analysis were selected. Based on these cut-off points, children were classified by each programme as susceptible or non-susceptible.

Across all programmes, susceptible children had significantly higher mean caries increment and % with new caries than non-susceptible children. For CAMBRA, compared with ≥moderate risk, ≥high risk had a higher sum of sensitivity and specificity (138% vs 118%). Both CAT and CAMBRA had extremely high sensitivity (99% and 94%) but low specificity (5% and 44%) in predicting ECC. Cariogram and NUS-CRA had a better balance between sensitivity and specificity. Compared with Cariogram, both versions of NUS-CRA models had a higher validity in predicted caries. Among all models, only the NUS-CRA comprehensive model reached a sum of sensitivity and specificity above 160%,[5] compared with 158% for the NUS-CRA screening model.

The performance of the programmes that generate continuous risk outcome (ie Cariogram and NUS-CRA) was also compared using ROC curves (Fig). Both the screening and comprehensive versions of NUS-CRA generated better prediction (higher AUC) than their Cariogram counterparts.

All models predicted mid-term (ie 12 months) caries increment better than short-term (6-month) and long-term (18-month) caries increment.

Discussion

The CAT and CAMBRA had an extremely high sensitivity but low specificity; almost all children with new caries were defined as high risk, but many children without new caries were also defined as high risk (ie a high false positive rate). Such overestimation may have stemmed from some of the classification criteria, of which some single factors/indicators alone were sufficient to justify a high-risk diagnosis. With high sensitivity, CAT and CAMBRA may be useful when failure to identify and treat any high-risk child is absolutely unacceptable and is the only concern. Nonetheless, the low specificity (overestimation of risk) leads to overtreatment and a waste of resources.

The Cariogram and NUS-CRA were superior in predicting ECC. The Cariogram is intended to assess risk at all age groups. A single programme applicable to all age groups would be convenient to clinicians. Nonetheless, the Cariogram has a high performance in adolescents and elders but a relatively unsatisfactory performance in children. It may be reasonable to incorporate some age-specific factors (eg milk bottle use) into Cariogram and recalibrate the built-in algorisms for young children. The NUS-CRA had a highly stable sensitivity and specificity in our sample and in Singaporean children,[4] supporting its use in Asian populations.

A periodical review of children's caries risk is recommended. Nevertheless, it remains unclear how

TABLE 1. Caries increment among children in different risk groups defined by each caries risk assessment programme (republished with permission of Elsevier, from Gao X, Di Wu I, Lo EC, Chu CH, Hsu CY, Wong MC. Validity of caries risk assessment programmes in preschool children. J Dent 2013;41:787-95.)

Caries risk assessment programme	No. of children	Mean±SD caries increment (change in No. of decayed, missing, or filled teeth [Δdmft])*	% with new caries (Δdmft >0)*	Relative risk (95% CI) for new caries*
Caries-risk Assessment Tool (CAT) [screening]				
Low risk	0	-	-	-
Moderate risk	18	0.17±0.51	11.1	1 (reference)
High risk	467	0.80±1.37	37.7	2.01 (1.06–2.52)
CAT (screening) excluding socioeconomic risk factors				
Low risk	0	-	-	-
Moderate risk	20	0.20±0.52	15.0	1 (reference)
High risk	465	0.80±1.38	37.6	1.81 (0.99–2.38)
CAT (comprehensive)				
Low risk	0	-	-	-
Moderate risk	11	0±0	0	-
High risk	474	0.79±1.37	37.6	-
CAT (comprehensive) excluding socioeconomic risk factors				
Low risk	0	-	-	-
Moderate risk	13	0.08±0.28	7.7	1 (reference)
High risk	472	0.79±1.31	37.5	2.20 (0.95-2.64)
Caries Management by Risk Assessment (CAMBRA) [screening]				
Low risk	68	0.10±0.39	7.4	1 (reference)
Moderate risk	77	0.13±0.50	7.8	1.04 (0.42-1.85)
High risk	340	1.06±1.51	49.1	2.39 (2.00-2.58)
CAMBRA (comprehensive)				
Low risk	137	0.20±0.76	10.9	1 (reference)
Moderate risk	85	0.27±0.68	16.5	1.31 (0.81-1.83)
High risk	263	1.24±1.58	56.7	2.34 (2.11-2.50)
Cariogram (screening)				
Very low risk	222	0.34±0.90	18.0	1 (reference)
Low risk	100	0.72±1.22	35.0	1.60 (1.24-1.93)
Moderate risk	112	1.02±1.31	53.6	2.05 (1.76-2.27)
High risk	44	2.07±1.63	86.4	2.57 (2.37-2.66)
Very high risk	7	3.43±3.82	71.4	2.37 (1.51-2.65)
Cariogram (comprehensive)				
Very low risk	268	0.34±0.88	18.7	1 (reference)
Low risk	109	0.77±1.21	42.2	1.77 (1.45-2.05)
Moderate risk	52	1.56±1.63	67.3	2.29 (1.99-2.48)
High risk	47	2.02±1.71	83.0	2.52 (2.30-2.63)
Very high risk	9	2.67±2.96	88.9	2.60 (1.94-2.71)
NUS-CRA (screening)				
Very low risk	249	0.25±0.77	12.4	1 (reference)
Low risk	68	0.56±1.04	32.4	1.80 (1.39-2.14)
Moderate risk	54	1.48±1.73	66.7	2.43 (2.19-2.57)
High risk	97	1.56±1.39	75.3	2.52 (2.38-2.61)
Very high risk	17	2.71±2.52	94.1	2.68 (2.43-2.72)
NUS-CRA (comprehensive)				
Very low risk	265	0.17±0.69	8.7	1 (reference)
Low risk	79	0.85±1.11	49.4	2.33 (2.08-2.50)
Moderate risk	42	1.26±1.38	66.7	2.52 (2.31-2.63)
High risk	49	2.10±1.63	83.7	2.64 (2.53-2.69)
Very high risk	50	2.18±1.87	94.0	2.70 (2.63-2.72)
All subjects	**485**	**0.78±1.36**	**36.7**	

* There is significant difference between risk groups with different ranks. The Chi-square test is used to compare proportions. The Fisher's exact test is used when the count in any cell of a 2x2 table is <5. The Tukey post-hoc test or independent *t*-test (as appropriate) is used to compare means when the distribution and homogeneity of variance is normal; otherwise, the Mann–Whitney *U* test or Kruskal–Wallis test (as appropriate) is used. Odds ratios and their confidence intervals are generated from logistic regression and converted to relative risk.

TABLE 2. Validity of caries risk assessment programmes in predicting caries (republished with permission of Elsevier, from Gao X, Di Wu I, Lo EC, Chu CH, Hsu CY, Wong MC. Validity of caries risk assessment programmes in preschool children. J Dent 2013;41:787-95.)

Cut-off point of predicted risk	No. of children	Mean±SD caries increment (change in No. of decayed, missing, or filled teeth [Δdmft])*	% with new caries (Δdmft >0)*	Relative risk (95% CI) for new caries (Δdmft >0)*	Sensitivity (%)	Specificity (%)	Sensitivity+ specificity (%)	Accuracy (%)
Caries-risk Assessment Tool (CAT) [screening]								
≥High								
Non-susceptible	18	0.17±0.51	11.1	1 (reference)	98.9	5.2	104	39.6
Susceptible	467	0.80±1.37	37.7	2.01 (1.06–2.52)				
CAT (screening) excluding socioeconomic risk factors								
≥High								
Non-susceptible	20	0.20±0.52	15.0	1 (reference)	98.3	5.5	104	39.6
Susceptible	465	0.80±1.38	37.6	1.81 (0.99–2.38)				
CAT (comprehensive)								
≥High								
Non-susceptible	11	0±0	0	-	100	3.6	104	39.0
Susceptible	474	0.79±1.37	37.6					
CAT (comprehensive) excluding socioeconomic risk factors								
≥High								
Non-susceptible	13	0.08±0.28	7.7	1 (reference)	99.4	3.9	103	38.9
Susceptible	472	0.79±1.31	37.5	2.20 (0.95–2.64)				
Caries Management by Risk Assessment (CAMBRA) [screening]								
≥Moderate								
Non-susceptible	68	0.10±0.39	7.4	1 (reference)	97.2	20.5	118	48.6
Susceptible	417	0.89±1.42	41.5	2.28 (1.83–2.53)				
≥High								
Non-susceptible	145	0.12±0.45	7.6	1 (reference)	93.8	43.6	138	62.0
Susceptible	340	1.06±1.51	49.1	2.38 (2.13–2.53)				
CAMBRA (comprehensive)								
≥Moderate								
Non-susceptible	137	0.20±0.76	10.9	1 (reference)	91.6	39.7	131	58.7
Susceptible	348	1.00±1.47	46.8	2.20 (1.91–2.40)				
≥High								
Non-susceptible	222	0.23±0.73	13.1	1 (reference)	83.7	62.9	147	70.5
Susceptible	263	1.24±1.58	56.7	2.27 (2.07–2.42)				
Cariogram (screening)								
≥38.5% chance of caries								
Non-susceptible	305	0.40±0.95	21.6	1 (reference)	62.9	77.9	141	72.4
Susceptible	180	1.41±1.67	62.2	2.16 (1.94–2.32)				
Cariogram (comprehensive)								
≥37.6% chance of caries								
Non-susceptible	304	0.41±1.01	20.7	1 (reference)	64.6	78.5	143	73.4
Susceptible	181	1.38±1.62	63.5	2.17 (1.95–2.35)				
NUS-CRA (screening)								
≥32.8% chance of caries								
Non-susceptible	307	0.28±0.79	15.3	1 (reference)	73.6	84.7	158	80.6
Susceptible	178	1.64±1.67	73.6	2.45 (2.32–2.54)				
NUS-CRA (comprehensive)								
≥35.2% chance of caries								
Non-susceptible	301	0.28±0.89	13.0	1 (reference)	78.1	85.3	163	82.7
Susceptible	184	1.59±1.58	75.5	2.47 (2.35–2.56)				

* Significantly different between susceptible and non-susceptible children. The Chi-square test is used to compare proportions. The Fisher's exact test is used when the count in any cell of a 2x2 table is <5. The independent *t*-test is used to compare means when the distribution and homogeneity of variance is normal; otherwise, the Mann–Whitney *U* test is used. Odds ratio and its confidence intervals are generated from logistic regression and converted to relative risk

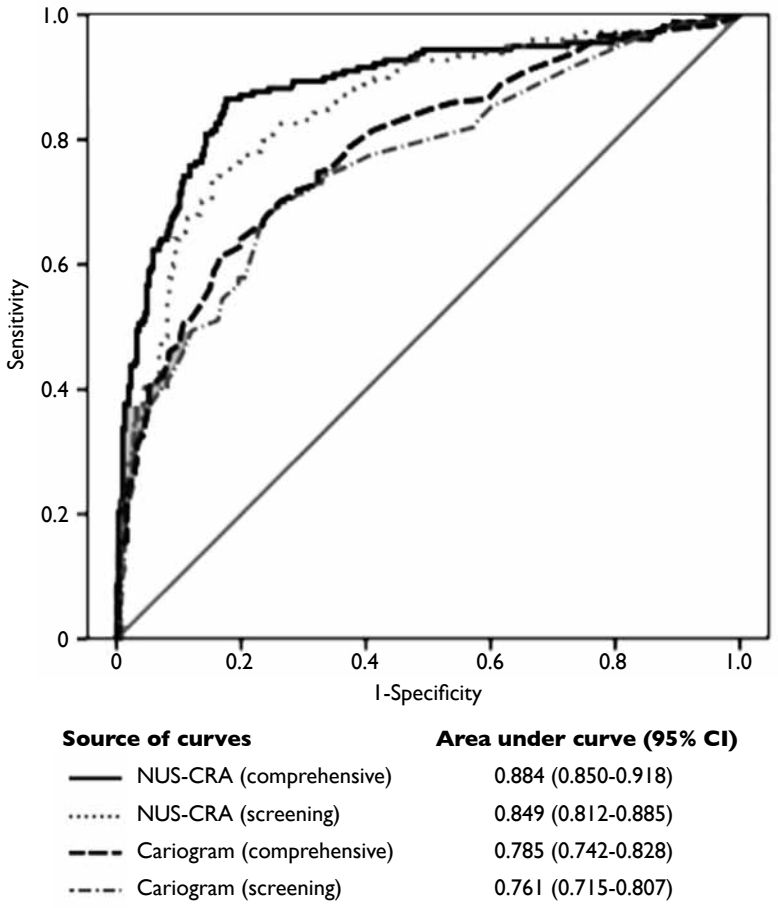

FIG. Receiver operating characteristic curves for programmes with continuous outcomes (republished with permission of Elsevier, from Gao X, Di Wu I, Lo EC, Chu CH, Hsu CY, Wong MC. Validity of caries risk assessment programmes in preschool children. J Dent 2013;41:787-95.)

frequent such review should occur. Across all CRA programmes, the prediction for 12-month caries increment was more accurate than for 6-month and 18-month outcomes. As caries is a chronic disease, a 6-month follow-up may be inadequate for the results of interaction of various factors to be manifested in the form of cavitation. In addition, young children are in the process of changing and establishing their habits, change in their risk profile over an 18-month period may be dramatic. Our findings support the timeframe adopted by Cariogram and NUS-CRA (ie prediction of risk in the coming year) and a periodical risk review on a 12-month basis. These findings will contribute to cost-effective caries prevention/intervention and optimised treatment planning.

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