

## RESEARCH ARTICLE

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# Doctor's Counselling Using Culturally Responsive Pamphlet Increased Mammogram Uptake among Malay-Muslim Women in Singapore: A Randomized Controlled Trial in a Primary Healthcare Clinic

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### Abstract

**Objective:** Malay-Muslim women experienced higher breast cancer mortality rate and lower mammogram uptake rate compared to other ethnic groups in Singapore despite equal access to health facilities. We aimed to increase mammogram uptake rate among Malay-Muslim women attending a primary healthcare clinic by providing doctor's counselling on mammogram and breast cancer. **Methods:** We conducted a randomized controlled trial to evaluate effectiveness of doctor's counselling using a culturally responsive pamphlet in increasing mammogram uptake among Malay-Muslim women attending the clinic. Those in intervention arm received 8-minutes doctor's counselling on mammogram and breast cancer while those in control arm received 8-minutes doctor's counselling on usual care – dietary care. We recruited 319 Malay-Muslim women aged 50-69 years old who have not undergone a mammogram in the past 2 years. We used Poisson regression to determine effectiveness of intervention in increasing mammogram uptake and to determine any change in knowledge, perceptions and faith-based beliefs on breast cancer and mammogram after counselling. **Results:** Those in intervention arm had 1.64 times higher mammogram uptake compared to those in control arm. Non-discernible changes in knowledge, perceptions and faith-based beliefs were observed, whereby only “I must have symptoms before I decide to go for mammogram” was significantly different between arms following counselling. **Conclusion:** Cue to action from doctor led to increased mammogram uptake among Malay-Muslim women. Future interventions to promote screening should include doctors and religious leaders to further improve mammogram uptake, and change knowledge, perception, and beliefs.

**Keywords:** Mammography- breast cancer- cancer screening- primary care- cues to action- Muslim- healthcare provider

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### Introduction

Higher breast cancer mortality rate among Muslims compared to other ethnic groups have been reported in many countries [1-3]. High mortality rate has been attributed to late detection of breast cancer among Muslim women [1, 2], although genetic predisposition to more aggressive subtypes among Malays has also been implicated in Singapore [4]. Singapore is home to 4.15 million residents. Malays, who are predominantly Muslims [5], comprise 13.5% of the population while Chinese and Indians comprise 74.0% and 9.0% of the population respectively [6]. Between 2013 – 2017, breast cancer mortality rate was 19.1 deaths per 100,000 population among Malay women, compared to less than

15.0 deaths per 100,000 among Chinese and Indian women [3]. Despite implementing mammogram screening programmes for 22 years [7], the ethnic gap in mortality rate has not closed [3].

To facilitate uptake of mammogram, Singapore made mammogram facilities available nationwide such as in polyclinics. Polyclinics are public healthcare facilities which provide primary healthcare services, including mammogram screening, at a subsidised rate [8, 9]. Polyclinics are highly utilised with more than half of the population attending polyclinics for chronic diseases, and majority of screeners completing their mammogram there. However, only 17.6% of those of Malay ethnicity reported attending mammogram within the last two years, compared to above 40.0% among their Chinese and Indian

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counterparts [10].

Cue from doctor to attend mammogram was reported to facilitate regular mammogram uptake in a recent community-based survey among Malay-Muslim women [11]. Cue from doctor was also associated with other cancer screening uptake including cervical cancer [12] and colorectal cancer [13] in the general population in Singapore. As such, designing an intervention centred around cues to action from doctor may improve mammogram uptake among Malay-Muslim women in Singapore.

However, evidence from intervention studies on effectiveness of cues from doctor in increasing mammogram uptake has been mixed. In a randomized controlled trial (RCT) in Canada, signed reminder letter from family physician was sufficient to encourage more mammogram uptake among previous screeners (adjusted Risk Ratio, aRR=1.41, 95% Confidence Interval, CI: 1.30, 1.54) than a standard reminder postcard [14]. Conversely, in a quasi-randomized pragmatic trial in Singapore, those that received intervention consisting of doctor's reminder and tailored education by patient navigator had 40% lower odds (adjusted Odds Ratio, aOR=0.60, 95%CI: 0.30, 1.30) of completing mammogram compared to those that received intervention consisting of tailored education only [15]. The authors attributed this result to lack of time and lack of standardisation in reminder delivered by doctor. Additionally, the authors hypothesised that more culturally responsive intervention may be necessary as those of Malay ethnicity were less likely than their Chinese or Indian counterparts to attend mammogram after similar intervention [15]. There is thus a need to determine the effectiveness of standardised culturally responsive counselling combined with cues from doctors in increasing mammogram uptake among Malay-Muslim women in Singapore.

In this study, we aimed to determine effectiveness of doctor's counselling on mammogram and breast cancer among Malay-Muslim women aged 50-69 years old using a RCT. We developed a pamphlet that is culturally-responsive to the Muslim faith and the Malay culture, in accordance to factors found to be associated with mammogram uptake in this community [11]. We standardised delivery of the cue to action for mammogram in a clinic-based setting through training and through use of the pamphlet.

We hypothesised that standardised culturally responsive counselling and cue from doctor to obtain mammogram screening will lead to an increase in mammogram uptake in the intervention arm, compared the control arm receiving cue from doctor on dietary care.

## Materials and Methods

This is a single blind RCT of Malay-Muslim women attending a polyclinic for common acute and chronic conditions between March 2021 to June 2021. We randomised days, using an online random list generator, so those attending polyclinic on the same day were allocated the same arm. This was done to reduce possible contamination bias should individuals of different arms

shared information about the project while waiting at the polyclinic.

Inclusion criteria were Singapore citizens or permanent residents aged 50-69 years who identified as Malay-Muslim women, while exclusion criteria were known history of breast cancer or benign lesions and having undergone mammogram in the last 2 years. The basis of exclusion was individuals with history of breast cancer or benign lesions could have received different screening interval recommendation by their doctors, and individuals who have undergone mammogram in the last 2 years were not eligible nor recommended for another mammogram according to the national guidelines [16].

We estimated 35% mammogram uptake in the intervention arm, based on a previous trial in a similar setting [15], compared to 20% in the control arm, based on baseline weekly mammogram uptake in the polyclinic. The sample size was rounded up to 350 (1:1 arm allocation) after accounting for a power of 80%, 5% two-sided level of significance, and 20% attrition rate.

### Standardised Counselling

We standardised counselling delivered through doctors' training by the Principal Investigator and through use of flipchart and pamphlet to guide counselling. To control for Hawthorne effect, the control arm received the same duration of 8 minutes counselling as the intervention arm but on dietary care using a flipchart (Supplementary Figure 1a-d). This is usual care in the polyclinic and does not influence mammogram uptake.

The intervention arm received counselling on breast cancer and mammogram using a bilingual pamphlet (Supplementary Figure 2a-b). The pamphlet showed a picture of a Malay-Muslim woman undergoing the procedure and was designed to be culturally-responsive addressing some factors found to be associated with mammogram uptake in this community [11]. During counselling, the doctor emphasized benefit of early detection, addressed misinformation on needing symptom for mammogram and addressed modesty concern through clarification on gender of radiographer. Education was also delivered to reduce perceived barriers towards mammogram and to help participant cope with breast cancer concerns such as fear of pain, and fear of diagnosis. Participants were advised to make an appointment at the mammogram screening counter.

### Outcome Measures

Primary outcome was radiographer-verified mammogram uptake in the polyclinic 6 weeks after final enrolment. Secondary outcomes were knowledge on treatment, knowledge of screening, perception of barriers and Punishing Allah Reappraisal (PAR) belief [17] (Supplementary Table 1) measured on a 7-point scale with "Strongly Disagree" at 1, "Neither Agree nor Disagree" at 4, and "Strongly Agree" at 7 in a questionnaire at baseline and at 6-weeks follow-up.

### Data Collection

Nurses screened for eligibility, explained the study, and obtained written consent. Participants then completed

a self-administered pre-intervention questionnaire available in English and Malay language. A doctor then conducts one-on-one counselling in a private consultation room. Follow-up was conducted via a telephone call to reduce potential COVID-19 exposure. Nurses called and administered post-intervention questionnaire in either language, 6 weeks after recruitment.

#### Data Analysis

Analyses were conducted using StataCorp. 2021. Stata Statistical Software: Release 17, College Station, TX: StataCorp LLC. We compared variables between arms at baseline using Chi-square test for categorical variables, t-test for numeric variables, and Wilcoxon rank-sum test for ordinal variables. Statistical significance value was set at  $p < 0.10$ .

We were guided by the intention-to-treat principle when assessing impact of the intervention. Poisson regression was used to determine difference in primary outcome – incidence rate ratio (IRR) of radiographer-verified mammogram attendance between intervention and control arms. Age was the only demographic characteristic which differed between arms ( $p$ -value=0.045). We adjusted for it in the main analysis of our primary outcome. As non-linear transformation of age did not improve prediction, age was analysed as a continuous variable.

We conducted exploratory factor analyses and reliability test to evaluate factor solutions and internal

consistency of our secondary outcome constructs. PAR, which was previously validated, was the only construct that demonstrated high internal consistency (Cronbach  $\alpha > 0.70$ ) and thus analysed as a grouped variable of low score (scores 3 – 12) compared to high score (scores 13 – 21) in subsequent analysis. Knowledge variables were analysed as single binary variables of “Disagree” (score  $\leq 4$ ) and “Agree” (scores 5 – 7), while perception variables were analysed as single binary variables of “Disagree” (score  $\leq 3$ ) and “Agree” (scores 4 – 7). We conducted Poisson regression for our secondary outcome to determine difference in knowledge, perception and belief at follow-up, IRR of “Agree” or high score between intervention and control arms, adjusting for baseline response.

Pearson goodness-of-fit test was used to check for overdispersion for all regression models. Although overdispersion was not detected, robust methods of estimating standard error was used as recommended [18].

#### Results

We screened 1000 Malay-Muslim women for eligibility, 319 of 400 patients were recruited (response rate 79.75%), and 21 participants were lost to follow-up (attrition rate, 6.58%; intervention arm 3.25% and control arm 9.70%) (Figure 1).

At baseline, participants randomized to intervention

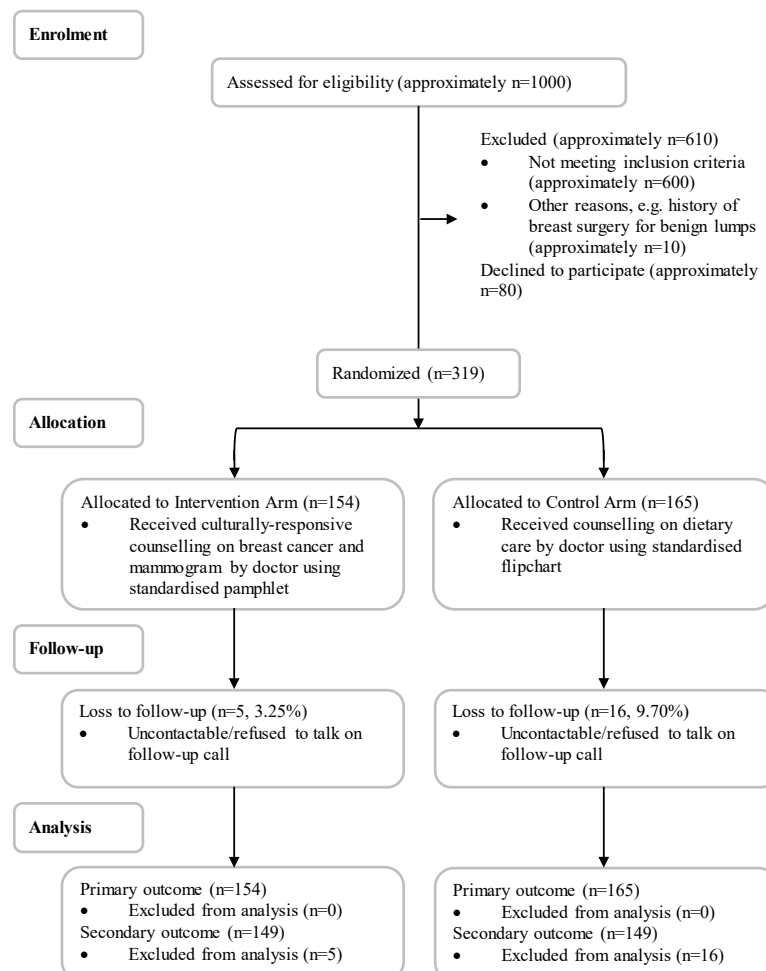


Figure 1. Study Flowchart CONSORT Diagram

and control arm were not significantly different except in their age (Table 1). Participants also had similar level of knowledge and beliefs. Median score differed only for two variables, whereby one, “Mammogram is embarrassing” was significantly different. At follow-up, only the median for “Mammogram is painful” was different between intervention and control arm, although not statistically significantly different ( $p=0.55$ ). Although the median for “I must have symptoms first before I decide to go for mammogram” was the same for both arms, Wilcoxon rank-sum test indicated that the spread was significantly different ( $p\text{-value}=0.04$ ). In general, most participants in both arms reported correct knowledge and perception for a high number of variables at baseline and at follow-up (Table 2).

Radiographers verified that 99 (31.03%) participants completed mammogram after doctor’s counselling. Compared to the intervention arm, where 60 (38.96%) completed mammogram, only 39 (23.64%) from the control arm completed mammogram. Mammogram uptake rate was 65% higher ( $IRR=1.65$ , 95%CI: 1.17, 2.31) in the intervention arm compared to the control arm. Adjustment for age difference between arms did not change IRR of mammogram uptake significantly (adjusted IRR, aIRR=1.64, 95%CI: 1.17, 2.30) (Table 3). Ten participants (6.49%) and five participants (3.03%) from the intervention and control arm respectively, postponed or cancelled their mammogram appointment.

Those that were lost to follow-up were excluded from our secondary outcome analysis. We observed limited differences in responses between arms following counselling. “I must have symptoms first before I decide

to go for mammogram” was the only variable that showed marginal significant difference at follow-up. Those in intervention arm were 63% more likely ( $IRR=1.63$ , 95%CI: 0.95, 2.81) to agree to needing symptoms, compared to those in control arm. Adjusting for baseline beliefs did not alter strength of association (aIRR=1.63, 95%CI: 0.95, 2.79) (Table 4).

## Discussion

This RCT aimed at determining the effectiveness of doctor’s counselling using a culturally responsive pamphlet in increasing mammogram uptake among Malay-Muslim women attending a polyclinic in Singapore. A 1.64 times higher mammogram uptake rate in intervention arm compared to control arm observed, supports our hypothesis that cue from doctor leads to mammogram uptake in this clinic setting.

Our finding that cue from doctor led to mammogram uptake in a polyclinic is consistent with a previous nationwide survey that found cue from doctor facilitated mammogram uptake among Malay-Muslim women [11]. The use of culturally responsive content enabled counselling to focus on factors associated with mammogram uptake within the short span of time, hence effectively increasing mammogram uptake in this community. Notably, cost reduction of mammogram was not part of our intervention package. Participants paid between S\$25 to S\$75, depending on regular subsidies that are available for them [8]. This highlights that while additional cost reduction in health interventions further increased mammogram uptake in a previous study

Table 1. Socio-Demographic Characteristics of Participants at Baseline by Arm

Socio-demographic Characteristics		Control Arm (N=165) n (%)	Intervention Arm (N=154) n (%)
Age (Mean $\pm$ SD)		61.27 (5.45)**	60.08 (5.02)
Married, n=319		110 (66.67)	112 (72.73)
Household Income, n=237			
	<S\$2,000	82 (62.12)	56 (53.33)
	S\$2,000 – S\$3,999	28 (21.21)	31 (29.52)
	S\$4,000 – S\$5,999	12 (9.09)	11 (10.48)
	$\geq$ S\$6,000	10 (7.58)	7 (6.67)
Highest Education Level, n=319			
	Primary Education	72 (43.64)	65 (42.21)
	Secondary Education	72 (43.64)	75 (48.70)
	Tertiary Education	21 (12.73)	14 (9.09)
Type of Housing, n=319			
	HDB 1-2 Rooms	23 (13.94)	25 (16.23)
	HDB 3 Rooms	53 (32.12)	36 (23.38)
	HDB 4 Rooms	59 (35.76)	54 (35.06)
	HDB 5 Rooms/Executive	30 (18.18)	39 (25.32)
Family History of Breast Cancer, n=319		18 (10.91)	14 (9.09)
Ever gone for Mammogram, n=311		92 (56.10)	79 (53.74)
Regular Mammogram Uptake, n=319		12 (7.27)	9 (5.84)

All data provided are number of responses and percentages except where indicated e.g. Age. P-value was derived using Chi-square except for age, where t-test was used. HDB, Housing Development Board. \*\*p-value < 0.05

Table 2. Median of Knowledge, Perception, and Belief Variables at Baseline and at 6-Weeks Follow-up by Arm

Variables			Control Arm	Intervention Arm	p-value
Knowledge	There are medical tests now that can detect breast cancer in its very early stage	Baseline	7	7	0.96
		Follow-up	7	7	0.76
	I must have symptoms first before I decide to go for mammogram <sup>^</sup>	Baseline	1	2	0.11
		Follow-up	1	1	0.04**
	I do not know how to make an appointment for mammogram <sup>^</sup>	Baseline	4	4	0.76
		Follow-up	1	1	0.19
	Early treatment prevents breast cancer from spreading to other parts of the body	Baseline	7	7	0.81
		Follow-up	7	7	0.32
	If the lump is small, it can be removed without removing the entire breast	Baseline	7	7	0.37
		Follow-up	7	7	0.4
	If breast cancer is detected early, chances of cure are very high	Baseline	7	7	0.81
		Follow-up	7	7	0.77
Perception	I am afraid of finding out if I have breast cancer if I go for mammogram <sup>^</sup>	Baseline	4	4	0.2
		Follow-up	4	4	0.45
	Mammogram is embarrassing <sup>^</sup>	Baseline	1	2	0.0002***
		Follow-up	1	1	0.54
	Mammogram is painful <sup>^</sup>	Baseline	4	4	0.64
		Follow-up	4	1	0.55
Belief	Punishing Allah Reappraisal+	Baseline	12	12	0.94
		Follow-up	12	12	0.81

All data provided are median. Correct knowledge is reflected by a maximum score of 7 except where indicated. <sup>^</sup> Correct knowledge or perception is reflected by a score of 1. + Correct belief is reflected by a score of 3. P-value was derived using Wilcoxon rank-sum test. \*\*\*p-value < 0.01, \*\*p-value < 0.05

Table 3. Number and Percentage that Completed Mammogram by Arm. Poisson regression models for radiographer-verified mammogram attendance, by arm.

Arm	Completed Mammogram, n (%)	Poisson Regression Models					
		Model A			Model B		
		IRR	95% CI	p-value	IRR	95% CI	p-value
Control	39 (23.64)	1	Ref		1	Ref	
Intervention	60 (38.96)	1.65	(1.17, 2.31)	p=0.004***	1.64	(1.17, 2.30)	p=0.004***

Model A, Poisson regression with radiographer-verified mammogram attendance as outcome variable and arm as design variable; Model B, Poisson regression with radiographer-verified mammogram attendance as outcome variable, arm as design variable, and adjusted for age as a continuous variable; IRR, Incidence Rate Ratio; Ref, Reference group; control arm. \*\*\*p-value < 0.01

among the general population [15], existing subsidies are sufficient to encourage mammogram uptake in this community.

Our study showed insignificant non-discernible differences in knowledge, perception and beliefs between arms following counselling despite significantly higher mammogram uptake in the intervention arm. While we expected some significant knowledge changes following counselling, this finding corroborates with literature on cues to action which indicates that behaviour change is supported if the cue received confirms one's existing knowledge [19], especially from a trusted source [20]. In our study, given the good existing knowledge among participants as reflected by their high baseline scores, it is possible that doctor's cue delivered in a personalised way activated and translated participant's existing knowledge into booking and completing a mammogram appointment. Nonetheless, the little insignificant difference observed

between arms following counselling could also be due to a ceiling effect [21], as reflected in high baseline scores for some variables (Table 3).

An unexpected finding in our study was a marginal statistically significant difference between arms for, "I must have symptoms before I decide to go for mammogram", whereby those in the intervention arm were more likely to agree to this statement (p=0.08). Such backfire effects have been reported in other health communication interventions which utilised misinformation refuting strategy. In a study on flu vaccination, participants that received handouts refuting misinformation identified more with the misinformation than those that did not receive the handout [22]. Repetition of the misinformation in our study pamphlet may have contributed to fluency, familiarity and perhaps acceptance of the misinformation when encountered again at follow-up. Furthermore, given that the occurrence of symptoms is at the centre of



Table 4. Poisson Regression Models for Knowledge, Perception, and Belief at Follow-up for Intervention Arm, with Control Arm as Reference Group.

Variable	Poisson Regression Models					
	Model C			Model D		
	IRR	95% CI	p-value	IRR	95% CI	p-value
There are medical tests now that can detect breast cancer in its very early stage	1	0.94, 1.06	0.98	1	0.94, 1.06	0.88
I must have symptoms first before I decide to go for mammogram	1.63	0.95, 2.81	0.08*	1.63	0.95, 2.79	0.08*
I do not know how to make an appointment for mammogram	0.74	0.50, 1.10	0.13	0.74	0.50, 1.08	0.12
Early treatment prevents breast cancer from spreading to other parts of the body	0.99	0.93, 1.05	0.8	1	0.95, 1.06	0.92
If the lump is small, it can be removed without removing the entire breast	0.99	0.94, 1.05	0.78	0.99	0.94, 1.05	0.81
If breast cancer is detected early, chances of cure are very high	1	0.95, 1.05	0.99	1	0.95, 1.04	0.9
I am afraid of finding out if I have breast cancer if I go for mammogram	0.99	0.79, 1.22	0.86	0.94	0.76, 1.17	0.59
Mammogram is embarrassing	1.17	0.58, 2.37	0.67	0.98	0.49, 1.95	0.94
Mammogram is painful	0.89	0.70, 1.11	0.3	0.89	0.71, 1.12	0.31
Punishing Allah Reappraisal	0.83	0.61, 1.13	0.24	0.84	0.63, 1.12	0.24

Model C, Poisson regression with knowledge, perception and belief after counselling as dependent variable and arm as design variable; Model D, Poisson regression with knowledge, perception and belief after counselling as dependent variable, arm as design variable and adjusted for responses before counselling as fixed effect; IRR, Incidence Rate Ratio; \*p-value<0.10

perception of illness for most [23], it may seem incoherent to seek healthcare in the absence of symptoms, particularly in a community such as this, which prioritizes the needs of their loved ones even when one is ill [24]. In the event of such coherence gaps, the misinformation may be preferred over the corrected information [22].

Of note, there was no difference in PAR beliefs between arms following counselling. This null finding was expected because PAR beliefs were not addressed in this intervention. Previous survey found those with high PAR or those that agree to appraising life difficulties as punishments by Allah as a means to cope, had higher odds of deferring mammogram uptake [11]. In our study, we provided the intervention arm with counselling on breast cancer and mammogram as means to cope with worries of breast cancer. PAR score at follow-up was not significantly different between arms suggesting that educating and suggesting mammogram as a solution to cope with worries on breast cancer without touching on PAR beliefs did not alter such beliefs held by participants as their coping response. Importantly, this highlights specificity of such belief and the need for religious intervention to change this belief.

#### Study Limitations and Strengths

Our study had the following limitations. As the survey at follow-up was administered by nurses via telephone call, social desirability bias could have influenced responses. However, participants were assured confidentiality of their responses and that there were no right or wrong answers as means to mitigate this bias. Also, our questionnaires were not validated among Malay-Muslim women attending

the polyclinic prior to data collection. As variables were derived from previous needs assessment among Malay-Muslim women [11], these variables have been found to be understandable in this community. Our study suggests that Malay-Muslim women attending the polyclinic have better knowledge on breast cancer and mammogram than their general community. Finally, this intervention was held during the COVID-19 pandemic, fasting month of Ramadan, and Hari Raya celebration. As such, participants cancelled or postponed their mammogram appointment, due to potential false reading caused by COVID-19 vaccination related risk of axillary lymphadenopathy, religious commitments, or family commitments. Therefore, mammogram uptake reported here may be an underestimation of real numbers.

Despite these limitations, our study has many strengths. Our primary outcome was verified by a radiographer. Our study had low attrition in both arms (intervention arm 3.25%, control arm 9.70%). Our study, which used a RCT design, has high internal validity. Finally, our study built on a previous nationwide needs assessment to deliver health educational content that is responsive to the culture of this community.

#### Public Health and Research Implications

Our study has several public health implications despite focusing solely on the Malay-Muslim women community in Singapore. It provides support for Singapore's national preventive health strategy (Healthier SG strategy) centring on trust towards their doctor. Through this strategy, individuals work with their doctor to make health plans including managing screening

schedules. Doctors provide cues and recommendation to help individuals follow their plan. Subsidies, such as for mammogram, are also available to aid individuals to follow their plan [25]. Our finding suggests that cues from doctor through this initiative will lead to an increase in mammogram uptake in this community and that further subsidies for mammogram, while available, may not be necessary should counselling be done effectively. Next, our study demonstrated that using a culturally responsive pamphlet for counselling is a robust way to encourage mammogram uptake amidst the pandemic. While globally mammogram screening reduced by 9% – 37% during the pandemic [26], we observed increased mammogram uptake in this community compared to its pre-pandemic rate. Our findings will also have public health implications for primary care settings with mammogram services in Malaysia and Indonesia. As Malay-Muslims in Singapore shares cultural roots with these countries, counselling using similar culturally responsive messages may increase mammogram uptake among individual of the Muslim faith visiting those facilities.

Our study has a few research implications. We found counselling on mammogram from a technical aspect, such as clarifying that mammogram can detect breast cancer in the absence of symptoms, to be insufficient to improve this knowledge. This highlights that needing symptoms before deciding to go for screening is not a misunderstanding on the concept of screening. Instead, this may reflect a decision made following a personal negotiation of one's priorities. Hence, further qualitative research may be necessary to better understand this perspective in-depth. Notably, our study also showed that doctor's counselling does not alter existing punishing beliefs. Religious interventions such as teachings by religious teachers may be necessary to change these punishing beliefs. Changes in such belief in combination with cue from doctor may further improve mammogram uptake. Future intervention should be conducted beyond primary health care setting, such as at places of worship, where religious and cultural beliefs can be incorporated. Such intervention should involve religious leaders to change punishing beliefs and encourage prioritisation of health, as well as doctor to provide cue to attend mammogram. Finally, our study also demonstrated the value of using findings from needs assessment to design interventions in a primary care setting. Similar research design can be used to tailor interventions for other health concerns among smaller ethnic groups where needs assessment among the general population may not comprehensively reflect needs of these groups.

In conclusion, our study demonstrated that doctor's counselling to attend mammogram using a culturally responsive pamphlet was effective in increasing mammogram uptake among Malay-Muslim women in a primary care setting. Further research to assess effectiveness of an intervention that use faith-based messages and engage religious leaders and doctors should be conducted in mosque settings in the community.

## Author Contribution Statement

MLW conceptualized the study. SL, SG and MLW developed study protocol. SG led development of pamphlet. SL collected study data. SG and SL analysed the data. All authors wrote the main manuscript text, reviewed and approved the manuscript.

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### Data Availability

Data supporting findings for this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

### Study Registration

This study has been registered in ClinicalTrials.gov (NCT06469567).

### Funding Statement

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### Ethical Statement

The National Healthcare Group Domain Specific Review Board (NHG-DSRB) approved this study (No. 2020/01244-SRF0001). Written informed consent was obtained from all participants in the study.

### Conflict of Interest

The authors declare no conflict of interest.

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