Cardiology in the Young

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Behavioural interventions to increase adherence to palivizumab prophylaxis in children with CHD

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Original Article

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Abstract

Objectives: Adherence to palivizumab prophylaxis programmes is crucial to protect infants with CHD against respiratory syncytial virus infections. We analysed the effectiveness of two nudge interventions in increasing adherence. *Methods:* Our study included 229 infants, and their caregivers, from five centers in Turkey in the 2020–2021 respiratory syncytial virus season. We randomly allocated caregivers to a control and two intervention groups. Caregivers in all groups were informed about the prophylaxis programme and provided a schedule. Additionally, caregivers in Intervention 1 were called two days before appointments (default bias) and were asked to plan the appointment day (implementation intention), whereas caregivers in Intervention 2 received biweekly text messages informing them about the programme's benefits (availability bias) and current adherence rate (social norm). *Results:* Caregivers in Intervention 1 had a significantly higher adherence rate than Control (97.3% versus 90.9%) ($p = 0.014$). Both interventions had a significant effect on participants in their first prophylaxis season ($p = 0.031$, $p = 0.037$). Families where the father was employed had a 14.2% higher adherence rate ($p = 0.001$). Every additional child was associated with a 2.2% decrease in adherence rate ($p = 0.02$). In control, ICU admission history was associated with an 18.8% lower adherence rate ($p = 0.0001$), but this association disappeared in intervention groups. *Conclusion:* This is the first prospective interventional study which, in the context of palivizumab prophylaxis, analyses the effectiveness of nudge interventions based on established cognitive biases by comparing randomly generated intervention and control groups. We found that default bias and implementation intention have significant effects on adherence.

Clinical trial, in the name and number "Adherence of palivizumab prophylaxis, NCT05778240" registered retrospectively. https://clinicaltrials.gov/ct2/show/NCT05778240.

Respiratory syncytial virus is the leading cause of acute respiratory tract infections, affecting almost every child at least once before they are 2 years old. Its complications are severe for children with cCHD, leading to hospitalisation rates three times more frequent and resulting in increased morbidity and mortality.[1]

For children with CHD, the benefits of palivizumab prophylaxis programmes are well-established.[1–6] Palivizumab is a monoclonal antibody, which needs to be administered monthly during the respiratory syncytial virus season (e.g. October to March) for full protection.

Achievement of higher adherence to the palivizumab prophylaxis relies critically on the actions of caregivers. Hence, an improvement in caregiver adherence behaviour will significantly contribute to the success of the prophylaxis programme. Choice architecture[7] reflects the fact that the way a choice problem is presented to decision-makers affects their choices without impeding freedom of choice. A fast-growing literature shows that cleverly designed choice architecture, based on established cognitive biases, can "nudge" decision-makers towards making better choices.[8–13]

In medicine, cognitive biases faced by caregivers and physicians, as well as the implications of nudge-based interventions, have been gaining importance in cardiovascular health protection,[14–17] influenza immunisation,[18–20] and organ donation,[21,22] as well as others.[23] Our paper contributes to this literature by utilising cognitive biases of caregivers to design nudge-based interventions in order to improve adherence to the palivizumab prophylaxis of 0–2-year-old infants.

We also consider the effect of a range of factors regarding the child and the caregiver on adherence to the prophylaxis programme, both in control and intervention groups.

Behavioural interventions

We utilise four well-established cognitive biases in designing two alternative nudge interventions. Via a randomised field study carried out in five geographically distinct regions of Turkey, we measure the effectiveness of each nudge intervention against a control group.

The first intervention is based on the notions of default bias and implementation intention. *Default bias* refers to a decision-maker's aversion to take action to change the default or to deviate from a predetermined action plan.[8] For example, making organ donation the default option increases participation in organ donation programmes.[21,22] Also, making generic drugs the default option in electronic health records increases their prescription by physicians.[24,25] *Implementation intention* refers to the phenomenon where specific planning regarding an action (by answering when, where, and how questions) increases a decision-maker's likelihood of carrying out that action. For example, asking voters to plan out how they will come to the election booth increases their likelihood of participation in an election (12) or asking people who need flu vaccination to plan out the day and hour they will come increases their adherence.[19]

The second intervention that we evaluate in this study is based on the notions of availability bias and social norm. *Availability bias*[26] refers to the effect of the ease with which a piece of information is recalled on the evaluation of its importance. Information that is easier to access is deemed to be more important by decision-makers. Furthermore, decision-makers judge the frequency of events they encountered in the recent past to be higher than actual. Studies have found availability bias in diagnosis of second-year fellows[27] and experienced physicians.[28,29] *Social norm* refers to a decision-maker's tendency to conform with the decisions and actions of a society or group they belong to. Increased prevalence of a norm or behaviour in the society increases the likelihood that the decision-maker will conform to it. For example, informing individuals that seatbelt usage among drivers is very common significantly increases seatbelt usage.[30]

Method

Study population

Our study population is 0–2-year-old infants with one or more of the following conditions: haemodynamically significant CHD, congestive heart failure, haemodynamically significant residual defects after corrective heart surgery, cardiomyopathy, and pulmonary hypertension. Upon consent from caregivers, children were included in the study and their medical information was recorded.

Study design and procedures

This is a prospective study that involves five children's hospitals from different geographical regions in Turkey (İstanbul, Sakarya, Kahramanmaraş, Sıvas, Van), producing a representative sample. Before the 2020–2021 respiratory syncytial virus season, in accordance with AAP guidelines,[31] paediatric cardiologists determined from among 0–2-year-old infants those eligible for palivizumab prophylaxis. Enrolment of participants in the study continued until the end of 2020. At the beginning of the study, 243 children with CHD were included. During the study, 14 participants were excluded because they lost touch or died. The study concluded with 229 participants. A flowchart in the Appendix illustrates the progress of all participants in the study. All vaccinations were carried out in the aforementioned hospitals. Informed consent forms were obtained from parents. Our study was approved by the Ethical Committee of the Kartal Koşuyolu Cardiac Center, with approval number 2020/14/413. The procedures followed in the study are in accordance with the Helsinki Declaration of 1964, revised in 2000.

In each hospital, caregivers were randomly allocated into one of three groups and were followed from October 2020 until April 2021. In all groups, as is standard practice in Turkey, caregivers were given a vaccination appointment card containing the dates of the prophylaxis appointments of their children for that season, as well as a telephone number they can call in case they need to change an appointment date.

Control

These caregivers received no additional intervention.

Intervention 1

These caregivers additionally received a telephone call every month two days before their appointment. To induce default bias, they were reminded that they had a set appointment. To induce implementation intention, they were asked to plan the day of their appointment. The following standard script was used in every hospital during the telephone call:

Hello, we are calling you because you are enrolled in the palivizumab prophylaxis research program. As you know, you have a vaccination appointment on [enter date] at [enter time]. To help you plan your day of appointment, we have a few short questions.

a. *At your appointment day, will you be coming to the hospital from home, or will you need to get permission from your workplace?*
b. *What kind of transportation do you plan to take to come to the hospital at your appointment day?*
c. *At what time do you plan to leave home or work to come to the hospital?*

Intervention 2

These caregivers were included in a WhatsApp (and if not available, SMS) text messaging group where they received biweekly text messages on respiratory syncytial virus, on additional risks it causes on children with CHD, and on benefits of adherence to the prophylaxis programme. The availability bias suggests that keeping such information "available" for the caregivers should increase the importance of adherence. Text messages also involved statements about the high number of caregivers that kept their appointments in the previous month, hence creating a social norm of adherence. As an example, below we present one of the text messages sent.

[Availability Bias]

Dear parent, almost every child is infected with the respiratory syncytial virus at least once before they reach the age of two. For children with congenital heart disease, a respiratory syncytial virus infection can lead to significantly more serious illnesses. Out of every two children with congenital heart disease, one has to be admitted to the intensive care unit due to respiratory syncytial virus infection. However, with regular vaccination every month, we can protect our children from the life threatening risks caused by respiratory syncytial virus infections.

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[Social Norm]

Dear parent, as of today families of 227 children in our five centers are regularly participating in the respiratory syncytial virus immunization program and protecting their children from respiratory syncytial virus infection. You are one of them. We congratulate you for the effort you put in for your child's health.

Study objectives and data collection

Our main variable of interest is each caregiver's adherence rate to the prophylaxis programme, defined as the total number of vaccinations received divided by the maximum number of vaccinations the child is eligible for. Children who were enrolled in the programme at the beginning of the respiratory syncytial virus season were eligible for five monthly doses. However, for a child who participated later, exceeded two years of age during the study, had an operation, became hospitalised, or was admitted to the ICU for a time period, the maximum number could be lower.

Our first objective was to test whether each of the two behavioural interventions led to an increase in the average adherence rate in comparison to the control group. To this end, participant adherence data were collected every month. We also collected additional data on children who (i) underwent surgery, (ii) was either hospitalised or admitted to ICU due to a variety of reasons, (iii) completed two years of age (since at that point, the state insurance stops paying for the palivizumab prophylaxis), and (iv) died or moved to another region.

A secondary objective of our study was to analyse factors that affect adherence. To this end, we asked participating families to fill out a survey (presented in the Appendix). Out of 229 participants, 209 (91%) filled out the survey. The questions focus on *(i)* the child's medical history (10 questions), *(ii)* family's socio-economic descriptives (8 questions), as well as *(iii)* questions about the mother and the father (6 questions each).

Statistical analysis

The statistical analysis was performed using STATA (Version 17. College Station, TX: StataCorp LLC). The descriptive statistics of the dataset are presented in Table 1. To compare the mean adherence rates of the control and intervention groups, the difference in means (t-test) was used. To comment on the role of confounding variables, as well as to test whether participants were randomly allocated to the three groups, multivariate linear regression models were employed. In addition, an interactive linear regression model was employed to see the conditional effect of ICU admission on adherence. Statistical significance was identified with p values less than 0.05.

Results

Among 229 children in the study, 71 were cyanotic (31%) and 158 had acyanotic (64%) CHD. The mean age was 8.5 months, 45.85% were female, 91.22% were born over 2000 g, 30.73% was born under 37 gestational weeks, 9.27% had additionally a chronic lung disease, 16.58% were previously hospitalised, and 16.10% had previous ICU admission due to lower respiratory tract infections. For families in our sample, median number of children is 3, mean maternal age is 31, median education level of the mother is middle school, and 31.71% of the fathers do not have a full-time job. Descriptive characteristics are shown in Table 1. Linear regressions that treat group membership as a dependent variable, and other traits of a participant as independent variables show that no traits of a child or caregiver have a significant effect on the probability of being assigned to an intervention group (Appendix). Hence, we conclude that our participants are randomly allocated to the three groups in terms of the analysed traits.

We first analyse the effect of our interventions on adherence. For caregivers in Control, average adherence rate was 90.9%. In comparison, average adherence rate in Intervention 1 was a significantly higher 97.4% ($p = 0.014$) (Fig. 1). In Intervention 2, average adherence rate was 94.2%, not significantly higher than Control ($p = 0.26$) (Fig. 1). To analyse the possible effect of previous experience with the prophylaxis programme, we group the participants into two. We assume that children who were younger than 285 days at the beginning of the interventions were in their first palivizumab prophylaxis season (these children were born around January 15, 2020 and since the palivizumab prophylaxis does not start before they are at least a month old, would most likely not participate in the prophylaxis programme in the 2019-2020 season). These constitute 148 of our 229 children (64.62%). In Control, Intervention 1 and Intervention 2, there are 49, 51, and 48 participants in their first prophylaxis season, respectively. For them, average adherence rate in the control group is 88.3%. In comparison, adherence rates are significantly higher with 97.7% and 97.1% in Interventions 1 and 2 ($p = 0.009$, $p = 0.018$) (Fig 2).

The remaining 81 of our 229 participants are in their second prophylaxis season. For these participants, average rates of adherence in Control, Intervention 1 and Intervention 2 are 95.4%, 96.7%, and 89.8%. The intervention group averages are not significantly different from Control ($p = 0.669$ and $p = 0.206$).

In line with our secondary objective, we also analysed which factors affect families' adherence to the prophylaxis programme. Table 2 presents factors that have significant association with adherence. First, families where the father is employed have a 14.2 percentage points higher average adherence rate than families where the father is unemployed ($p = 0.0001$). A second important factor affecting adherence is the number of children in the family. Every additional child is associated with a 2.2 percentage point decrease in adherence rate ($p = 0.02$). Third, caregivers of children with a birth weight of greater than 3000 g have a 5.4 percentage points higher adherence rate than others ($p = 0.013$).

Finally, caregivers of children with a history of ICU admission have 7.1 percentage points lower adherence rate than others ($p = 0.016$). To better understand this association, we also separately analysed the effect of ICU admission in each one of our three groups. In Control, ICU admission is significantly associated with an 18.8 percentage point decrease in adherence rate ($p = 0.001$). On the other hand, in Interventions 1 and 2, ICU admission has no significant effect on adherence (Fig 3).

We also analysed factors such as whether the family was informed about respiratory syncytial virus, found the prophylaxis programme important or not, where they lived, how far they needed to travel to come to the hospital, difficulties they faced in accessing the prophylaxis, family size, number of children going to school, family income, smoking, father and mother's age, education level, work status of mother, marital status, and health condition. These variables were found not to have significant association with adherence rate.

Discussion

The literature demonstrates that adherence to the palivizumab prophylaxis is effective in prevention of respiratory syncytial virus-

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Table 1. Descriptive statistics

	Control	Treatment 1	Treatment 2	Overall
Sex	35 (44.30%) Male	43 Male (57.33%)	46 Male (61.33%)	124 Male (54.15%)
	44 (55.70%) Female	32 Female (42.67%)	29 Female (38.67%)	105 Female (45.85%)
Mean age (in days) at the first vaccination	252	224	256	244
Birthweight (Grams)	30 (44.78%) > 3000	26 (%38.24) > 3000	31 (%44.29) > 3000	87 (%42.44) > 3000
	30 (44.78%) 2000–3000	33 (%48.53) 2000–3000	30 (%42.86) 2000–3000	93 (%45.37) 2000–3000
	5 (%7.46) <2000	5 (%7.35) < 2000	8 (%11.43) < 2000	18 (%8.78) <2000
Birth week	52 (77.61%) 37–40	43 (63.24%) 37–40	47 (67.14%) 37–40	142 37–40 (69.27%)
	12 (17.91%) 35–37	16 (23.53%) 35–37	12 (17.14%)35–37	40 35–37 (19.51%)
	2 (2.99%) < 35	5 (7.35%) < 35	11 (15.71%) < 35	18 (8.78%) < 35
Chronical lung disease	3 (4.48%) Yes	8 (11.76%) Yes	8 (11.43%) Yes	19 (9.27%) Yes
	61 (91.04%) No	59 (86.76%) No	61 (87.14%) No	181 (88.29%) No
Hospitalisation	53 (79.10%) Never	59 (86.76%) Never	58 (82.86%) Never	170 (82.93%) Never
	13 (19.41%) At least once	9 (13.24%) At least once	12 (17.14%) At least once	34 (16.58%) At least once
Intensive care	56 (83.58%) Never	59 (86.76%) Never	56 (80.00%) Never	171 (83.41%) Never
	10 (14.93%) At least once	9 (13.24%) At least once	14 (20.00%) At least once	33 (16.10%) At least once
		HOUSEHOLD		
Mother education	33 (49.25%) ≤ Primary	27 (39.71%) ≤ Primary	27 (38.57%) ≤ Primary	87 (42.44) ≤ Primary
	24 (35.82%) Middle– High School	26 (38.24%) Middle– High School	32 (45.71%) Middle– High School	82 (40.00%) Middle– High School
	9 (13.43%) ≥ University	15 (22.06%) ≥ University	11 (15.71%) ≥ University	35 (17.07%) ≥ University
Father education	27 (40.30%) ≤ Primary	14 (20.59%) ≤ Primary	23 (32.85%) ≤ Primary	64 (31.22%) ≤ Primary
	27 (40.30 %) Middle– High School	32 (47.06%) Middle– High School	32 (45.72%) Middle– High School	91 (44.39%) Middle– High School
	11 (16.42%) ≥ University	21 (30.88%) ≥ University	14 (20.01%) ≥ University	46 (22.43%) ≥ University
Number of children in the household	13 (21.31%) 1	24 (36.92%) 1	12 (17.91%) 1	49 (25.39%) 1
	36 (59.02%) 2–3	33 (50.77%) 2–3	43 (64.18%) 2–3	112 (58.03%) 2–3
	8 (13.11%) 4	7 (10.77%) 4	5 (7.46%) 4	20 (10.36%) 4
	4 (6.56%) > 4	1 (1.54%) > 4	7 (10.45%) > 4	12 (6.22%) > 4
Father employment	8 (11.94%) No job	9 (13.24%) No job	8 (11.43%) No job	25 (12.20%) No job
	9 (13.43%) Part–time	7 (10.29%) Part–time	11 (15.71%) Part–time	27 (13.17%) Part–time
	44 (65.67%) Full time	48 (70.59%) Full time	48 (68.57%) Full time	140 (68.29%) Full time

The category of "No Answer" was excluded from the table.

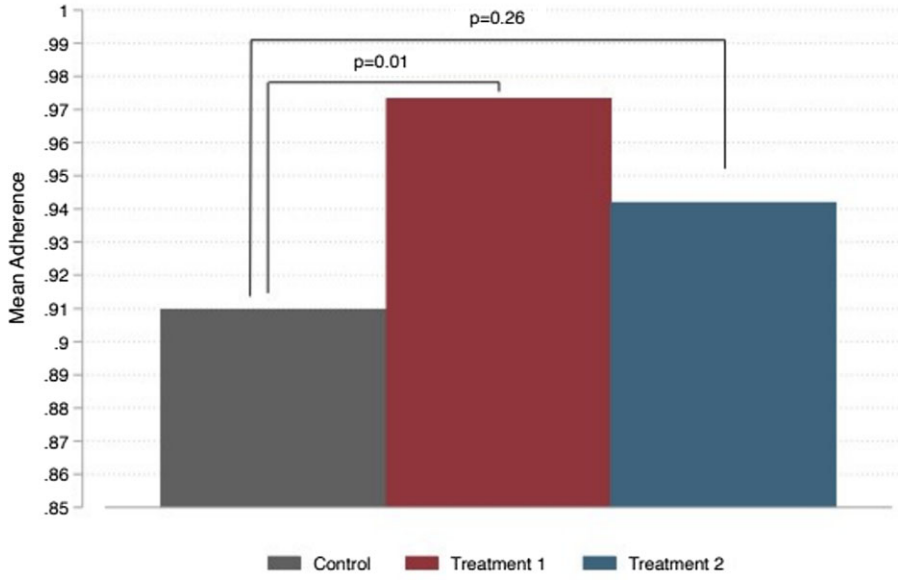

Figure 1. The adherence rates in Control, Intervention 1, and Intervention 2 were, respectively, 90.9%, 97.3%, and 94.2%. In Intervention 1, the adherence rate was significantly higher than Control.

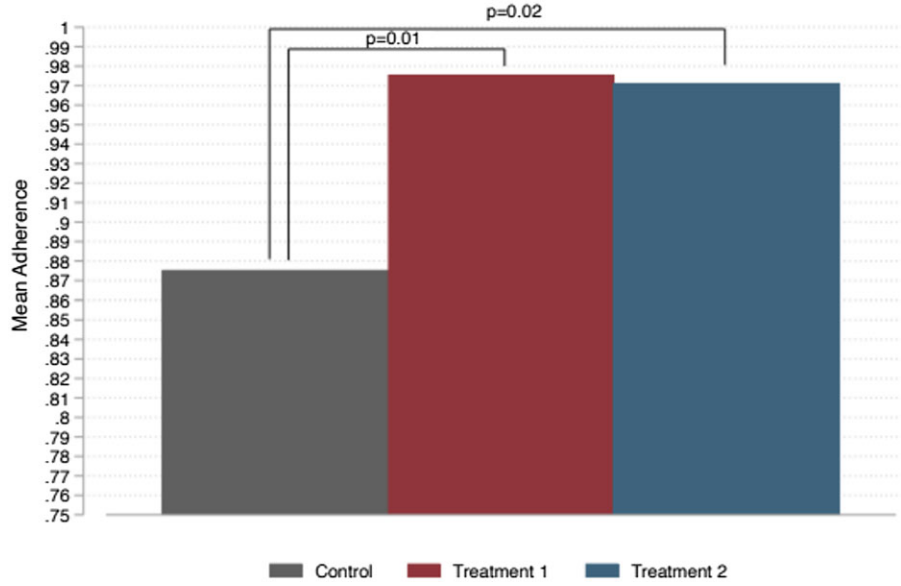

Figure 2. In case of participants in their first prophylaxis season, the adherence rates in both intervention groups were higher than Control.

based diseases. Lower adherence rates are associated with a higher risk of hospitalization,[2,3,5,6,32] respiratory-related ER visits,[33] and ICU admission.[4] However, full adherence is rarely achieved.

A number of studies analyse factors that affect adherence to palivizumab prophylaxis.[5,34–37] Among these, perceptions and information about benefits, emotional and time costs, child's age and sex, family size, and parents' education are forthcoming. Two literature reviews additionally mention a handful of studies that retrospectively analyse the effect of institutional strategies on adherence.[38,39] These authors argue that there is a need for prospective studies which use control or contemporaneous comparison groups and formal statistical analysis to analyse the effectiveness of systematically designed interventions to increase adherence. Indeed, the literature is lacking on this front.

We are only aware of two prospective studies that analyse the effect of institutional interventions on adherence. The first implemented an education programme for families of neonates and demonstrated an increase in adherence in comparison to the previous respiratory syncytial virus season.[40] The other implemented an outreach programme for parents and primary care physicians but did not find a significant increase in adherence.[41] Neither study compared randomly generated intervention and control groups. Instead, they were before-and-after (*i.e.* pre-post) studies. Indeed, randomised experiments are necessary in understanding whether an institutional intervention is effective.[42]

Our study contributes to the literature by providing the first randomised study that measures the implications of adherence to two behavioural interventions. Furthermore, both interventions are based on well-established cognitive biases in the literature. Initiated by a number of seminal studies,[26,43] behavioural economics systematically studies cognitive biases decision-makers exhibit and their implications in the effectiveness of behavioural interventions. As a result, behavioural studies have been flourishing in a number of fields including medicine, as discussed in the Introduction, and medical institutions have been initiating Nudge Units as in the case of the University of Pennsylvania Medical School.[17]

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Table 2. Linear regression estimates of adherence

Adherence	Coefficient	Std. Error	T-value	P-value	[95% Conf	Interval]	Sig
Father employment	0.142	0.033	4.28	0	0.076	0.208	***
Number of children	−0.022	0.01	−2.31	0.022	−0.041	−0.003	**
Intensive care	−0.071	0.029	−2.43	0.016	−0.128	−0.013	**
Birthweight	0.054	0.021	2.51	0.013	0.011	0.096	**
Constant	0.856	0.04	21.36	0	0.777	0.935	***
Mean dependent var	0.941			SD dependent var		0.154	
R-squared	0.213			Number of obs		174	
F-test	11.464			Prob> F		0.000	
Akaike crit. (AIC)	−189.399			Bayesian crit. (BIC)		−173.604	

***p < 0.01.
**p < 0.05.
*p < .1.

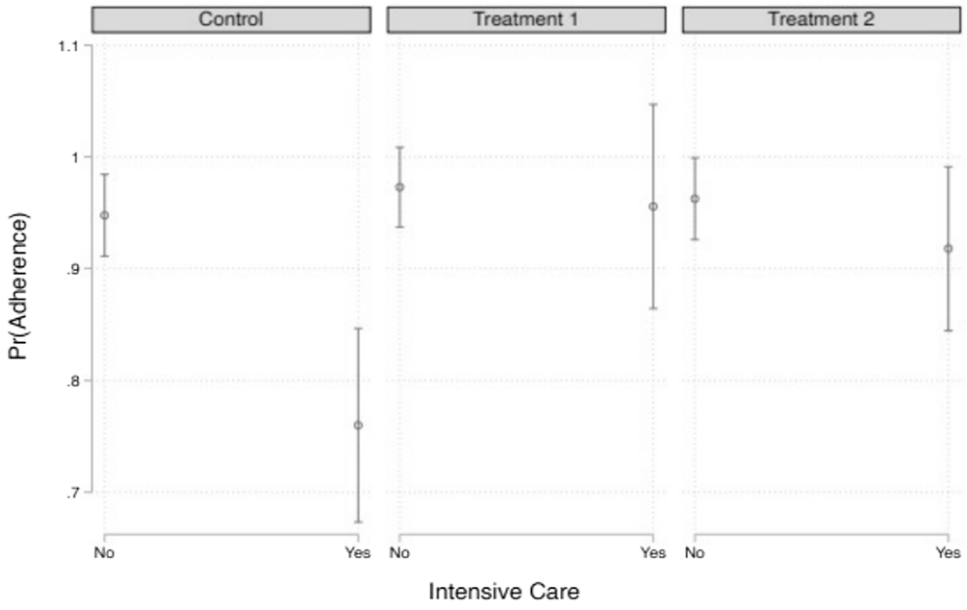

Figure 3. The effect of ICU admission history on adherence rate in Control, Intervention 1, and Intervention 2. The effect is significant only for children in Control.

Our study is the first to analyse, via a prospective study that randomly allocates participants to three groups, the effectiveness of two nudge interventions based on four established cognitive biases. Particularly, we are not aware of any study that brings together default bias and implementation intention (in case of Intervention 1) as well as availability bias and social norms (in case of Intervention 2) to design a nudge intervention. Similarly, the literature lacks comprehensive studies that test effectiveness of interventions when statistically controlling for child and family characteristics. Finally, our study is the first to bring together five geographically diverse medical centres in Turkey. Previous studies on Turkish data are retrospective and focus on a single medical centre.[37] With the exception of a retrospective study on Polish data,[44] studies in other countries also focus on a particular centre or region.

When surveyed about possible ways to increase adherence,[45] physicians' top three recommendations are (in order of decreasing popularity) additional education materials, frequent reminders from the hospital, and education of the child's family. Our interventions are in line with these recommendations, though, we do more than sending reminders or providing educational material. We also find on the overall sample that education materials (Intervention 2) are not as effective as a phone call before appointment (Intervention 1).

First, our study finds that participants in their first prophylaxis season present a much stronger response to nudge interventions. For this group, both our interventions lead to a significant increase in adherence while on the overall, only Intervention 1 leads to a significant increase in adherence. Furthermore, in our Control group participants in their second prophylaxis season exhibited higher adherence than participants in their first prophylaxis season (though the difference is only significant at 90% confidence level). This is in line with studies that point to the importance of child age and highlight that interventions should particularly target younger children.[5,36,44]

Our measure of adherence is one of the few predominant ones in the literature.[39] One popular alternative (especially in studies on health benefits of the prophylaxis programme) is to measure adherence rate as the percentage of participants who are in full

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compliance with the prophylaxis programme. Since this measure codes participants as either a zero or a one (full compliance or not), it is obviously more crude than ours. But using it does not change our findings qualitatively.

We also analyse factors that affect families' adherence to the palivizumab prophylaxis, and how they interact with our two interventions. Among these, the first significant factor is whether the father has a full-time job. Given that almost 75% of our sample mothers are homemakers, fathers are the sole breadwinners in the family. This finding is consistent with recent studies on Turkey which state that women's labour force participation is low, especially for families with young children.[46] We therefore believe that the primary mechanism through which father's job status affects adherence is via family income. Even though the Turkish state provides the prophylaxis programme free of charge for all qualifying children until 2 years of age, family income makes a difference in additional costs such as transportation, especially considering that 82% of the families in our sample have a monthly total income of less than 5000 TL (roughly 678 USD at the time of the intervention). The previous literature also identifies transportation and time costs as an important determinant of adherence.[34,35]

We find another important factor decreasing adherence to be the number of children in the family. For families with a higher number of children, the additional effort required to follow the prophylaxis programme has a higher opportunity cost. Another important factor turns out to be the child's birth weight where families of babies with a birthweight of over 3000 g show higher adherence. To the best of our knowledge, ours is the first study to find an association between birthweight and adherence.

Finally, we find that, while there is negative association between a history of ICU admission and adherence to palivizumab prophylaxis in the control group, this is not the case in our intervention groups. This highlights a second and previously unseen contribution of our interventions. In addition to having a direct positive effect on adherence, the interventions also serve to offset the negative effect of ICU history on adherence. This might be due to a closer follow-up of participants as well as provision of more information on the benefits of adherence.

Limitations

One important limitation of our study is that it was carried out during the COVID-19 pandemic. We believe the pandemic might have led to a higher baseline adherence rate (i.e. the adherence rate for the control group). Indeed, the rates of adherence we see in the previous literature are lower.[37,40] One possible mediator for this effect is a higher awareness of and anxiety due to upper and lower respiratory diseases on the part of the caregivers due to COVID-19. Additionally, in the survey part of our study, we have a question about the factors that make it more difficult for the caregivers to follow appointments. Among these are listed COVID-19 as well as others such as transportation, prescription, time allocation, etc. Caregivers did not state COVID-19 as an important factor making adherence more difficult for them. Hence, we expect that overall, COVID-19 led to an increase in the baseline adherence rate.

The COVID-19 pandemic also limited the number of centres that were able to participate in our study, hence limiting the number of participants. This was because some hospitals were declared to be centres for the pandemic, and had to limit or cease some of their operations regarding CHD.

Conclusion

Our study highlights the importance of basing the design of nudge interventions on the established literature on cognitive biases. Such nudge interventions provide an effective way of increasing health benefits of treatments at a comparatively lower cost and invasiveness. Once effective interventions are identified, future studies should focus on the trade-offs between the benefits and costs of each intervention.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951124024946.

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Competing interests. None.

Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees (Ethical Committee of the Kartal Koşuyolu Cardiac Center, with approval number 2020/14/413).

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