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CANCER SCREENING INVITATIONS IN THE DEVELOPING WORLD*

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Abstract

Over the last decades, the implementation of effective screening programs has starkly reduced cervical cancer mortality in High-Income Countries (HICs). As a result, roughly 90 percent of cervical cancer deaths nowadays occurs in low- and middle-income countries (LMICs), where nationwide cancer screening programs are nearly absent because of infrastructural barriers. In LMICs that have the capability to implement such programs, participation is often low because of information gaps, cultural, and socio-economic barriers. In this paper, we report results of a field experiment that we conducted within the national screening program of the Republic of Armenia to test whether the screening invitation strategies usually employed in high-income countries (HICs) could enhance screening uptake even in LMICs, despite the aforementioned barriers. We find that the dispatch of invitation letters significantly enhances participation, especially when followed by reminders. Different message frames have no impact. Our empirical results suggest that the implementation of invitation strategies employed in HICs could help to overcome commonly perceived barriers towards screening in LMICs and enhance screening participation.

JEL codes: I12; I15; I18; C93; D91.

Keywords: cervical cancer screening; randomized controlled trials; invitation letters; reminders; framing.

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1. Introduction

Cervical cancer is the fourth most frequent cancer in women, accounting for roughly 10% percent of all female cancers diagnosed in 2018 and a mortality rate of 8.2/100,000 women at risk (Globocan, 2018). Besides morbidity and mortality, cervical cancer exerts substantial negative social and economic effects on patients, their families, and society as whole, mostly related with high treatment expenses and shrunk productivity (Campos et al., 2017; Ekwueme et al., 2008; Oliva et al., 2005).

Due to its specific mono-causal genesis, that requires a long persistence of human papillomavirus infection (HPV) of the uterine cervix, cervical cancer is one of the most preventable neoplastic diseases. Thanks to the implementation of organized population-based screening programs (through either a cytology-based approach or HPV testing), a large decline in cervical cancer incidence and mortality has been documented in high-income countries (HICs) over the last decades (Arbyn et al., 2009; Lăără et al., 1987; Peto et al., 2004). For instance, recent European evidence suggests that women attending organized screening experienced a cervical cancer mortality reduction ranging between 41% and 92% with respect to non-attenders (Jansen et al., 2020).

Meanwhile, around 90% of deaths from cervical cancer occurs in low- and middle-income countries (LMICs). This unpleasant outcome has been mostly attributed to the lack of infrastructures and scarce healthcare resources to implement adequate national screening programs (Gakidou et al., 2008; Lazcano-Ponce et al., 1999; O'Donovan et al., 2019; Rao, 2012; Sankaranarayanan et al., 2001). Even when such programs are in place, participation is often much lower in LMICs than in HICs. Thus, the governments of LMICs that implement population-based cervical cancer screening programs face an important policy challenge to increase the uptake of these programs through various interventions.

Several communication and invitation strategies have been introduced in HICs to boost cancer screening uptake. For instance, there is robust evidence that invitation letters and reminders substantially increase women's participation in cervical cancer screening programs in HICs (Decker et al., 2013; Eaker et al., 2004; Radde et al., 2016; Tavasoli et al., 2016). Invitation letters carry a substantial informational value and can make it easier for recipients to evaluate the costs and benefits of screening (BIT, 2014). Furthermore, invitation letters can increase recipients' awareness of the programs in place, underscore their eligibility and emphasize the importance of participating in these programs (see Getsel et al., 2017 and the references therein). In addition, reminders can help recipients to overcome their limitations in self-control, memory, and attention, inducing them to attend the screening once their awareness of the program is enhanced through the invitation letters (e.g., Altmann and Traxler, 2014; Sunstein, 2014).[1] Besides letters and reminders, alternative message frames can also be used to enhance the salience of the information contained in the invitations and, therefore, stimulate recipients' behavioral response (Bertoni et al., 2020).

Unfortunately, despite the documented benefits that the aforementioned strategies exert on stimulating participation in cervical cancer screening programs in HICs, we are not aware of any randomized trial testing whether they could help to enhance cancer screening participation in LMICs.

[1] On top of cancer screening, reminders have been successfully used to promote virtuous health behaviors in other relevant domains such as dental care (Altmann and Traxler, 2014), clinical appointments and referral for health services (Macharia et al., 1992), blood pressure screening (McDowell et al., 1989), influenza vaccination (Milkman et al., 2011), and physical exercise (Calzolari & Nardotto, 2017).

Nonetheless, there are sound reasons to believe that the efficacy of invitation letters and reminders may be considerably undermined in LMICs as compared to HICs. Cultural concerns such as the shame of sickness (since the virus is mostly transmitted through sexual contact), stigmatization, religious taboos, superstition and the like (Ndikom & Ofi, 2012; Vu et al., 2018) can play an important role in limiting participation in spite of the amount of information provided to potential attendees by the invitation letters and of the potential behavioral biases that reminders may help to overcome. Socio-economic barriers such as poverty, lack of spousal support, distrust in the healthcare system and fear of the out of pocket expenses associated with the treatment of the cancer[2] (Ebu et al., 2015; Islam et al., 2017; Mabele et al., 2018; Vu et al., 2018) can also play a similar role.

The present study reports the results of a randomized controlled trial that we carried out in May-July 2019 to evaluate the effectiveness of a set of low-cost invitation interventions on women's participation in a national cervical cancer screening program . The trial was implemented in Shirak, the poorest region of the Republic of Armenia. With respect to the status-quo – an opportunistic screening regime where women aged 30 to 60 can voluntarily show up at their general practitioner (GP from here onwards) to be prescribed a free screening once every three years – we assess the effects of three interventions:

i. sending personalized invitation letters to women's home addresses to invite them to screen at a given date;
ii. reinforcing the invitation with subsequent reminders sent in proximity of the screening date;
iii. using ad-hoc frame manipulations of the invitation letters and reminders.

On this latter point, the invitation letters and reminders used in our experiment contain either a neutral message or are based on two ad-hoc frame manipulations:

i. a "negative" frame, that provides salient and enhanced information about the potential negative consequences of forgoing a check-up;
ii. an "other-regarding" frame, that enforces the importance of the check-up for the sake of fulfilling the expectations of one's family members.

The health persuasion literature in psychology (Rothman & Salovey, 1997) put forth the hypothesis based on Prospect Theory (Tversky and Kahneman, 1981) that gain-framed messages are more effective at promoting prevention behaviors (such as vaccines), while loss-framed messages at promoting detection behaviors (such as screening). This prediction has gained some empirical support in the context of disease detection behaviors (O'Keefe & Jensen, 2009). Moreover, results from a randomized controlled trial in Italy (Bertoni et al., 2020) show that letters containing loss-framed information about the risks of foregoing participation in screening programs enhance take-up. This evidence suggests that negatively framed invitation letters and reminders should outperform the neutral ones in terms of enhancing women's participation.

As for the "other-regarding" frame, social scientists have amply documented that individuals are endowed with altruistic preferences and are willing to sacrifice their own welfare to benefit others (Becker, 1976; Simon, 1993). Consequently, an invited woman may undertake a screening test to

[2] In many LMICs, including Armenia, out of pocket payments — formal co-payments, informal payments to the staff of the medical institutions and payments for services — remain the main funding source for the health sector in Armenia (Akkazieva & Jowett, 2013; Lavado et al., 2018; Richardson, 2013).

make her family members happy. Moreover, the "other-regarding" frame manipulation can also activate feelings of guilt aversion, whereby individuals strive to fulfill other's expectations about their behavior (Battigalli & Dufwenberg, 2007; Battigalli et al., 2013; Charness & Dufwenberg, 2006). Both considerations imply that "other-regarding" invitation letters and reminders should be more effective in stimulating participation in the screening program relative to neutral ones.

Prima facie evidence about the overall positive effect of our intervention can be assessed by considering the evolution of the monthly screening take-up rate in Shirak (black) and the Rest of Armenia (RoA - gray) during 2018 (dashed) and 2019 (solid), reported in Figure 1. The graph also overlays the Difference-in-Difference (DiD – dotted) estimates obtained by subtracting the Shirak-RoA difference in monthly take-up in 2018 from the same difference for each month of 2019.

Until April, the two areas of the country display trends in screening participation in 2019 that are fully comparable to the ones recorded in 2018. Instead, in the period highlighted by the vertical bars between May and July 2019, when our experiment was in place, screening take-up in Shirak increases by at least one order of magnitude – from 1 to 2.5 percent – while it remains stable in the rest of Armenia. In addition, the trends in the two areas are again comparable to the ones observed in 2018 in the months following the experiment.

When we zoom in and focus on the effectiveness of the various invitation strategies that we have experimentally introduced in Shirak, we find that the dispatch of invitation letters substantially increases the take-up of the program. Furthermore, invitations are considerably more effective when reinforced by subsequent reminders. Finally, neither the frame of the letter nor that of the reminder exert any effect on participation.

Our results illustrate how easily implementable and low-cost changes in the management of cancer screening program invitations can significantly increase screening in LMICs, with positive consequences for the reduction of cervical cancer mortality.

The rest of the paper is structured as follows. We present the institutional setting in Section 2 and the experimental design and procedures in Section 3. Section 4 introduces our data and we illustrate our empirical methods in Section 5. Section 6 presents our results and conclusions are in Section 7.

2. Institutional Setting

The Republic of Armenia is an upper middle-income country in transition in the South Caucasus, with a GDP per capita of around $4,238 in 2018 (World Bank, 2019), relatively high levels of poverty (23.5% of the population is below the national poverty line; Armstat, 2019), and a share of Government expenditure devoted to public health lower than the world average (Lavado et al., 2018).[3]

Non-communicable diseases (NCDs) – cancer, diabetes, cardiovascular and chronic respiratory diseases – account for roughly 93% of all deaths in the country, out of which 28% is attributed to cancer (WHO, 2018). High mortality and morbidity of NCDs come at a substantial (direct and indirect) economic cost of roughly 362.7 billion Armenian drams (AMD) per year, which constituted 6.5% of

[3] In 2014, the unweighted world average was around 11.8% as compared to roughly 7% in Armenia (16). According to WHO estimates such a stark difference is preserved in subsequent years as well (an interested reader can refer to WHO's Global Health Expenditure Database (http://apps.who.int/nha/database, retrieved on 22.03.2020).

the GDP in 2017 (Farrington et al., 2019). The Government of the Republic of Armenia is taking active steps to minimize the harm imposed by NCDs.

In January 2015, the Ministry of Health (MoH) launched the first national cervical cancer screening program in the Republic of Armenia, offering a free of charge Pap smear test slot to women aged 30-60 every three years.

The target of the program is to have 35% of the eligible women screened every three years, and MoH has defined national guidelines for screening implementation as well as for determining how screen-detected anomalies should be treated. While these features resemble the typical characteristics of organized programs (Miles et al., 2004), participation in the program is still opportunistic. Despite the availability of population registers, there are no organized invitations and eligible women freely visit their GP to express their intention to undertake a cervical cancer screening test, which usually takes place at their reference primary healthcare facility.[4] Since the launch of the screening program, MoH has informed the eligible women about the screening program through publications in popular press, TV and radio shows, dissemination of information through general practitioners, social media, booklets and banners.

In the first phase of the program, implemented between January 2015 and December 2017, 26.8% of the eligible population underwent screening – less than the 35% target. The second phase of the program has started in January 2018 and will last until December 2020. As of February 2019, the participation rate of the eligible population was still low, around 9%. For this reason, we teamed up with the Health Project Implementation Unit (HPIU) of MoH and the Armenia National SDG Innovation Lab (a joint initiative of the UN and the Government of the Republic of Armenia) to design and test ad-hoc interventions aimed at stimulating women's voluntary participation in the national cervical cancer screening program at relatively little monetary cost for the health authorities.

The randomized controlled trial was run in the region of Shirak, located in the North-Western part of the country. We chose Shirak following two considerations. First, participation of women living in Shirak during the first phase of the program, until December 2017, has been lower than in the rest of Armenia (21% vs. 27%). Second, with 42.4% of the resident population below the national poverty line the region has the highest poverty rate in the country. This implies that anticipating cancer detection with screening may substantially help households to save higher out-of-pocket cancer treatment costs associated with a later diagnosis, as well as to reduce the foregone earnings due to reduced productivity (or complete inability to work) associated with the onset of the disease.

3. Experimental design and procedures

The experimental protocol was approved by the IRB of the Department of Economics – University of Venice Ca' Foscari, and we registered the trial in the American Economic Association's registry for randomized controlled trials (AEARCTR-0004243).

[4] Patients can choose their primary healthcare provider following the Health Care Law introduced in 1996, albeit 90% of Armenians are ascribed to the local primary care provider according to residence (Armstat, 2012). If the primary healthcare facility does not have the capacity to undertake the test, the patient is directed to another primary healthcare facility.

We designed the experiment to test the effects of three strategies to enhance screening participation with respect to the status quo of opportunistic screening and exposure to soft advocacy campaigns.

The first strategy consists of delivering letters inviting a random sample of women targeted by the program to visit the general practitioner for the Pap smear test at closed-date, pre-booked appointments. Each woman receiving an invitation was assigned to a one-week slot to visit the general practitioner at any time she wanted. Subjects were randomly allocated across invitation weeks independently of treatment allocation.

The second manipulation reinforces invitation letters with reminders, that we sent to a random sub-sample of the invited women close to the screening date.

The third strategy concerns manipulations of the frame of the invitation letters and reminders. We tested three alternative frames of letters and reminders:

i. A "baseline" message, that provides general information about the national cervical cancer screening and the health benefits of taking the Pap smear test.
ii. A "negatively framed" message that saliently states the potential negative consequences of foregoing a check-up.
iii. An "other-regarding framed" message that leverages participation on the basis of a "do it for your beloved ones" argument.

For women receiving both the letter and the reminder, we let "other-regarding" and "negatively framed" invitation letters be followed by analogously framed reminders, while neutral letters are succeeded either by neutral or by "negatively framed" or "other-regarding" reminders. Copies of each letter and reminder type are reported in the Appendix.

As a result, in February 2019 we randomized a total of 36,508 women eligible for cervical cancer screening and enrolled in the ten largest healthcare centers of the Shirak region into eight invitation treatment groups (N=2,600*8=20,800) and one no-invitation control arm (N=15,708). The resulting allocation is depicted in Figure 2.

To enhance balancing, the randomization was stratified by GP. We randomly selected a different number of invited subjects for each GP in order to reproduce in the invited pool the same distribution of patients by GP that is observed in the target population, and assigned the remaining subjects to the control group. Then, we randomly and evenly allocated subjects within the invited pool by GP to one of our eight treatments.[5]

Stratified individual randomization exposes us to the threat of downward biases in our treatment effects due to potential spillovers across subjects in different treatment groups within each GP. We

[5] For instance, consider a GP practice enrolling 5% of the women in the eligible population, that is 36,508*5%=1,825 eligible women. From this set we would randomly select 20,800*5% = 1,040 women to receive an invitation, and randomly allocate 1,040/8=130 of them to each invitation type. The remaining 1,825-1,040=785 eligible women enrolled at this GP practice would be allocated to the control group. The allocation was carried out by us using STATA's random number generators. Given this allocation, we estimate a minimum detectable effect of 2.01 percentage points for pairwise comparison of the take-up rate across any two treatment groups of size N = 2,600 using two-tailed T-tests with power 1-β=0.8, significance α=0.05, and assuming a standard deviation of the outcome of 0.259 (observed in Shirak during the pre-intervention period).

could have alternatively chosen to block-randomize invitations by GP, village or hospital. We have chosen not to proceed like this for three reasons:

i. More than 70% of subjects live in the same urban area (Gyumri), and no information on boroughs of residence was available;

ii. Given that there are only 80 GPs and 10 hospitals in our data, we would have had few groups over which to randomize, and could have had to pay high prices in terms of balance and cluster-robust inference;

iii. GP offices are located next to each other in hospitals, generating threats of spillover across GPs within primary healthcare facilities.

Overall, 20,800 letters and 13,000 reminders were sent for invitations to screen in the period May 27-July 5. We randomly invited subjects to show up in one of the experimental weeks independently of treatment group allocation, to make sure that there was no seasonality imbalance across treatment groups. Letters were supposed to be delivered by the mail company in charge of the dispatch three weeks before the appointment week (starting from May 6), and reminders one week before the appointment.

Reassuringly, after the randomization was carried out we have also verified that the treatment groups are well balanced in terms of few available pre-determined observable characteristic (age, residence in urban or rural area, quarter of birth) – see Appendix Table A1– as well as in terms of the invitation week – only for invitees, see Appendix Table A2 – supporting the internal validity of the design.

4. Data

We used three data sources. First, population-level registers of the target population of the program were provided by the MoH. The ideal target population should have been composed of women resident in Shirak and affiliated with the 10 largest primary healthcare units in the region, aged 30-60 at the time of randomization (February 2019) and who had not undergone cervix cancer screening over the previous three years (i.e., since February 2016). Unfortunately, the final experimental population differs from the ideal one because individual-level data on screening is only available since May 2017. Therefore, we have been able to exclude from the sample women who already undertook a test between May 2017 and February 2019, but eventually we cannot rule out the possibility that some women in our sample underwent screening between February 2016 and May 2017. However, as we randomly allocate subjects across groups this is not an issue for internal validity. In addition, our main findings are also confirmed when we only consider subjects who turned 30 from May 2017 onwards, for whom the likelihood of screening between February 2016 and May 2017 is zero because they were not yet part of the target population. The data contain information on date of birth, that we use to compute age at the time of randomization, GP, hospital of affiliation, and residence in urban or rural area. The data from one doctor were incomplete, therefore we have removed the data for her 312 patients from the sample, which leaves us with a final sample of 36,196 women on whom all statistical analyses are carried out. Given that the randomization is stratified by GP, this does not compromise the internal validity.

Second, we use data on actual letter delivery at women's address from the mail company in charge of delivering letters.

Third, we exploit data on participation in the screening program, that come from two sources. On the one hand, we distributed special forms to the GPs in the primary healthcare units involved in the experiment. Between May and July 2019, GPs were requested to collect information on the date of the visit and the identity of those patients expressing willingness to undertake the Pap smear test. If the patient refused to take the test conditional on arriving at the primary healthcare facility or had issues incompatible with the test, the practitioners were requested to indicate this in the form. The participation was recorded from May 6 until July 19, when our data collection was over. On the other hand, the individual-level participation data collected through the forms were further compared with the internal records of the primary healthcare facilities for further verification. In case of an inconsistency between the two information sources, the internal records of the primary healthcare facilities were given superiority.

5. Empirical methodology

We estimate the Intention-To-Treat (ITT) effects on screening take-up of each invitation strategy vis-à-vis the control group by estimating the following linear regression model using Ordinary Least Squares (OLS):

$$Screened_{ij} = \alpha_j + \sum_{g=1}^{8} \gamma_g (Group_{ij} = g) + \varepsilon_{ij} \quad (1)$$

In Equation (1), *i* stands for individual, *j* for GP and *g* for treatment arm. The dependent variable $Screened_{ij}$ is a dummy variable equal to one if individual *i* underwent screening, and to zero otherwise. The explanatory variables comprise α_j, a vector of GP fixed effects, that we included because the randomization is stratified by GP, as well as a set of eight dummy variables ($Group_{ij} = g$), g = 1, …, 8, equal to one if subject *i* belongs to treatment group *g*, and to zero otherwise. Finally, ε_{ij} is a random error term. The estimates of coefficients γ_g, g = 1, …, 8, are reported in column (1) of Table 1. Given the binary nature of the dependent variable, we estimate standard errors that are robust to heteroscedasticity.

As we fail to detect heterogeneous effects of the different frames of letters and reminders, we also estimate a more parsimonious model that pools together all "letter only" treatments as well as all "letter and reminder" treatments. The specification adopted is as follows:

$$Screened_{ij} = \alpha_j + \gamma_1 LetterOnly_{ij} + \gamma_2 LetterReminder_{ij} + \varepsilon_{ij} \quad (2)$$

In Equation (2), $LetterOnly_{ij}$ is a dummy variable equal to one if subject *i* was only dispatched an invitation letter, and to zero otherwise, while $LetterReminder_{ij}$ is a dummy variable equal to one if subject *i* was dispatched both an invitation letter and a reminder, and to zero otherwise. The estimates of coefficients γ_1 and γ_2 are reported in column (2) of Table 1.

At this stage, it is also worth considering that only roughly 6 out of 10 letters dispatched were eventually delivered. As a result, the ITT effects of being *dispatched* a given invitation type underestimate the Treatment-On-the-Treated (TOT) effects of *receiving* a given invitation type. Hence, we exploit the availability of data on actual letter and reminder delivery to estimate the TOT effects by estimating the following equation with Two-Stage Least Squares:

$$Screened_{ij} = \alpha_j + \gamma_1 LetterOnlyReceived_{ij} + \gamma_1 LetterReminderReceived_{ij} + \varepsilon_{ij} \quad (3)$$

In Equation (3), $LetterOnlyReceived_{ij}$ is a dummy variable equal to one if subject *i* was dispatched an invitation letter only and received the letter, and to zero otherwise, while

$LetterReminderReceived_{ij}$ is a dummy variable equal to one if subject i was dispatched both an invitation letter and a reminder and both were received, and to zero otherwise.

The two dummies $LetterOnly_{ij}$ and $LetterReminder_{ij}$, that describe the randomly assigned invitation type of each subject i, serve as instrumental variables for the corresponding endogenous variables for reception of the assigned invitation type.[6]

6. Results

6.1.Main results

Figure 3 reports the percentage of screened subjects by treatment groups with 95 percent confidence intervals. We see that screening participation is significantly higher in each treatment group than in the control. Moreover, groups assigned to receive letters and reminders (the blue bars) generally display higher take-up rates than groups assigned to letter-only treatments (the red bars). Finally, there are no relevant differences in participation neither across treatment groups that received differently framed invitation letters only, nor across treatment groups that received differently framed letters and reminders.

These descriptive results are confirmed by the statistical analysis reported in Table 1. In Column (1) we report the Ordinary Least Squares (OLS) estimates of the Intention-To-Treat (ITT) effects of being dispatched each invitation type vis-à-vis the no invitation control group. Treatment effects range between 6.9 and 10.8 percentage points, a three- to five-fold increase with respect to the 2.1 percent take-up in the control group.

In addition, we confirm the absence of statistically relevant differences across treatment groups that receive differently framed invitation letters only (the p-value for joint equality of all "letter only" treatment effects is 0.62), as well as across treatment groups that receive differently framed letters and reminders (the p-value for joint equality of all "letter and reminder" treatment effects is 0.23).

As a consequence, in Column (2) we present results of a more parsimonious model that respectively pools all "letter only" and all "letter and reminder" treatments together. We see that, compared to the control group, being dispatched a letter with no reminder increases the take-up by 7.3 percentage points on average, while the dispatch of a letter and reminder combination boosts participation by 9.8 percentage points on average. The 2.5 percentage points difference between the "letter only" and the "letter and reminder" treatments is highly statistically significant ($p<0.01$).

Finally, Column (3) of Table 1 reports the TOT effects on screening take-up of *receiving* a letter only or a letter and reminder combination. Consistent with our discussion in Section 5, it shows that TOT effects are roughly 1.6 times larger than the corresponding ITT effects of Column (2). This finding highlights that our intervention could have generated even larger effects if more letters had been effectively delivered.

[6] The estimates of the first-stage equations are reported in Appendix Table A3. The Kleibergen-Paap F statistic for under-identification of the TSLS model is equal to 11,606, well above the rule-of-thumb value of 10 to safeguard against weak instruments. We also find that the first stage effects are larger for subjects residing in rural than in urban areas, as in the former areas it might be easier for postmen to ask for help in locating the invitee's address than in the latter ones (the first stage effects are 0.787 vs. 0.575 for letter reception and 0.742 vs. 0.485 for letter and reminder reception). This result suggests that the compliers of our instruments are more likely to belong to the rural population.

6.2. Additional results

We have verified the robustness of our findings to changes in the specification of our empirical model and in the selection of our sample. We present all results in the Appendix, focusing on the ITT effects of letter only invitations and letter and reminder invitations presented in Column (2) of Table 1. We have implemented the following additional analysis:

i. We worry about dependence of the error term across patients of each GP and allow for clustering of standard errors by GP. Results are reported in Appendix Table A4 and are in line with our baseline.

ii. We take into account the binary nature of the dependent variable and use logit or probit models instead of OLS estimation. Results are reported in Appendix Table A5 and are in line with our baseline.

iii. We only consider subjects who turned 30 from May 2017 onwards, for whom the likelihood of previous screening between February 2016 and May 2017 is zero because they were not yet part of the target population. Results are reported in Appendix Table A6 and are in line with our baseline.

We also tested for heterogeneous effects by age (above and below 50 – the standard threshold age for breast cancer screening program eligibility) and across urban and rural residents. Results are reported in Appendix Table A7 and display a pattern that is comparable across the various sub-samples considered.

7. Conclusions

Promoting screening participation is a key factor to fight cervical cancer. This holds true especially in LMICs, where the mortality rate of this neoplastic disease continues to be excessively high relative to HICs. Despite the potential benefits, the implementation of large-scale screening programs as well as the participation in the existing ones remain very low in LMICs, thus requiring "novel methods for improving uptake and implementation of cervical screening" (O'Donovan et al., 2019).

Results of our randomized controlled trial confirm the effectiveness of organized over opportunistic participation in population-based cervical cancer screening programs in the Republic of Armenia. The country context was ideal for implementing our experiment because Armenia has the necessary infrastructure to run an effective nationwide screening program – as well as a supporting Government – but the implementation of an organized screening program is still at its infancy, in particular as far as the involvement and invitation of targeted women is concerned. Our results reinforce the view that a relatively low-cost intervention of simply sending invitation letters and reminders to the target population can help to substantially enhance program participation, in spite of the cultural and socio-economic barriers that are often blamed for the low screening participation in LMICs.

Several mechanisms can explain the effects of invitation letters and reminders documented in our experiment. For instance, despite advertisement campaigns promoted by the Government and health authorities, women can still lack institutional and operational information about the screening program. In this respect, invitation letters and reminders can stimulate participation by raising the awareness of the program, emphasizing the importance of undertaking the screening and making the information on how to participate in it more accessible. In addition, by providing a precise time

window for participating in the program, reminders can mitigate behavioral biases (e.g. self-control, limited memory, inattention) that either prevent women from screening or induce them to unnecessarily postpone the decision.

While recent studies conducted in HICs document that the frame of the invitation letters (in particular when enhancing information on the potential risks of not screening; see Bertoni et al., 2020) affects cancer screening uptake, the "loss" and "other regarding" frame manipulations used in our experiment do not exert any significant effect on Armenian women. In our view, rather than being caused by cultural characteristics driving the psychological interpretation of (ad-hoc) framed messages, this empirical discrepancy is more likely related to the institutional setup. The implementation of a new population-based program, with women receiving an official invitation letter for the first time in their life, *per se* represents a strong policy intervention that focuses public attention on the importance of cervical screening, and probably crowds out any further effect of letter frame.

It is also worth noting that, for the time being, we only observe short-term outcomes, i.e., participation in the screening program within our limited observation window (May-July 2019). A concern in this respect could be that the effects we are picking up shall not be interpreted as suggesting that invited subjects screen more, but instead that these subjects are anticipating screenings that would have nonetheless been carried out at a later date. While anticipation of screening is *per se* a positive result, we notice that, had that been the case, we should have observed a decline in take-up in Shirak with respect to the rest of Armenia and to the corresponding trends for 2018 when the experiment was over. This is something that does not appear in the monthly regional data reported in Figure 1. Data on screening take-up as well as on health outcomes over the next few years will help to shed light over the long-run effects of our intervention.

Finally, despite the encouraging results, our study also suggests that the efficacy of the proposed health policy intervention depends to a large extent on the efficacy of other basic and fundamental infrastructures, such as the correct information on the addresses eligible patients live at. In our experiment, out of 10 letters dispatched, only 6 were eventually delivered, implying that the effect of the intervention could have been even stronger if a higher fraction of women had effectively received the invitation to screen.

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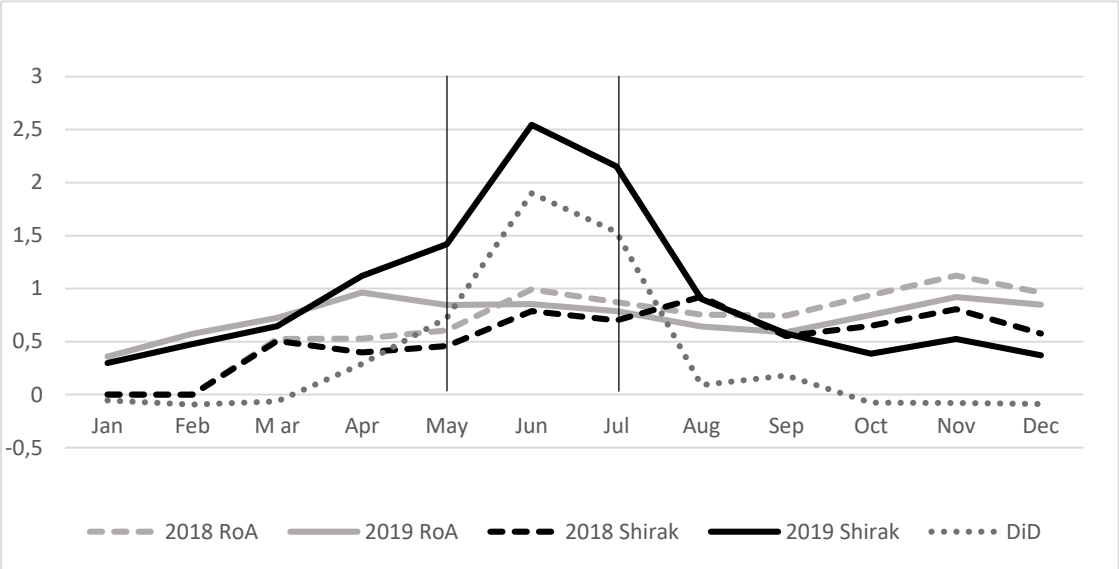
Figures and Tables

Figure 1. Monthly screening take-up in 2018 and 2019. Shirak vs. Rest of Armenia (RoA)



Notes: the figure reports the monthly screening take-up rate in Shirak and the Rest of Armenia in each month of 2018 and 2019. The Difference-in-Difference (DiD) estimates reported are obtained by subtracting the Shirak-RoA difference in monthly take-up in 2018 from the same difference for each month of 2019. The experiment took place in Shirak between May and July 2019 – as highlighted by the vertical bars. Given that monthly data on the eligible population is not available, the take-up rate is computed as the number of screened women over the number of eligible women as of January 2015, when the program began. *Source:* Ministry of Health screening registers.

Figure 2. The Structure of the Experiment

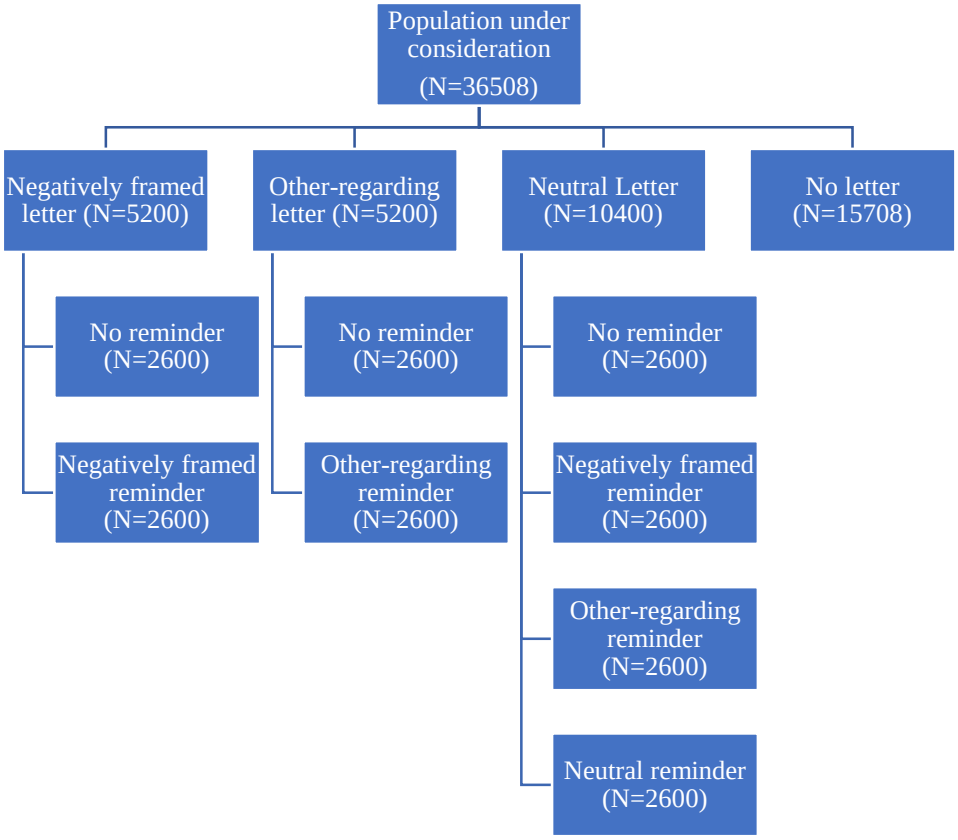
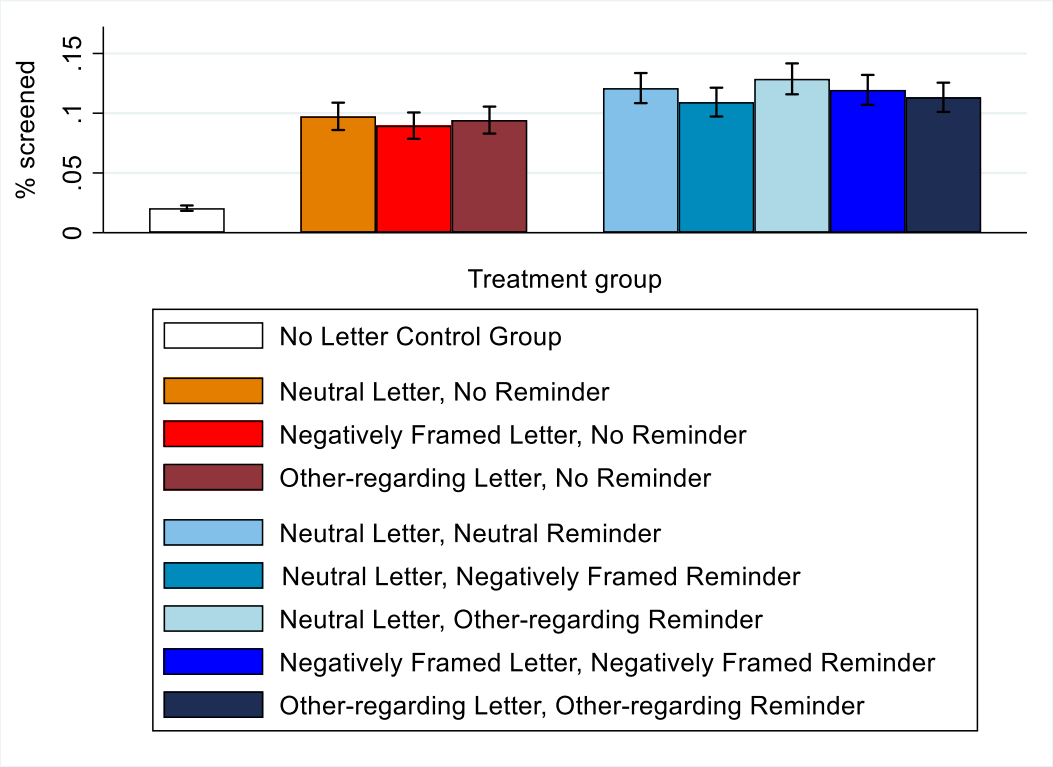


Figure 3. Screening participation by treatment group



Notes: the graph reports the percentage of screened subjects by treatment group with the associated 95 percent confidence interval. Sample size for each group is reported in Figure 2.

Table 1. The effects of different invitation types on take-up

	(1)	(2)	(3)
Dependent variable	Screening participation	Screening participation	Screening participation
Parameter estimated	ITT - treatment dispatched	ITT - treatment dispatched	TOT - treatment received
Estimation method	OLS	OLS	TSLS
<u>Letter only invitations</u>		0.073***	0.118***
		(0.004)	(0.006)
Neutral Letter, No Reminder	0.077***		
	(0.006)		
Negatively Framed Letter, No Reminder	0.069***		
	(0.006)		
Other-regarding Letter, No Reminder	0.074***		
	(0.006)		
<u>Letter and reminder invitations</u>		0.098***	0.181***
		(0.003)	(0.006)
Neutral Letter, Neutral Reminder	0.100***		
	(0.007)		
Neutral Letter, Negatively Framed Reminder	0.089***		
	(0.006)		
Neutral Letter, Other-regarding Reminder	0.108***		
	(0.007)		
Negatively Framed Letter, Other-regarding Reminder	0.099***		
	(0.007)		
Other-regarding Letter, Other-regarding Reminder	0.093***		
	(0.006)		
P-value of an F-test for joint equality of all treatment effects	<0.01	<0.01	<0.01
P-value of an F-test for joint equality of all "letter only" treatment effects	0.62		
P-value of an F-test for joint equality of all "letter and reminder" treatment effects	0.24		
Mean Outcome, No Letter Control Group		0.021	

Notes: Column (1) reports the OLS estimates of the ITT effects each treatment on screening participation. Column (2) reports the OLS estimates of the ITT effects of being dispatched an invitation letter only or being dispatched a letter and a reminder combination on screening participation. Columns (3) reports the TSLS estimate of the TOT effects of receiving an invitation letter or receiving a letter and a reminder combination on screening participation. The dependent variable, the parameter identified, and the estimation method are reported at the top of each column, while the mean outcome for the no letter control group is reported at the bottom. All models control for GP fixed effects. Sample size for each group is reported in Figure 2. Heteroscedasticity-robust standard errors reported in parenthesis. *: p<0.1; **: p<0.05; ***: p<0.01.

Online Appendix for the paper "Cancer Screening Invitations in the Developing World: Evidence from Armenia", by Armenak Antinyan, Marco Bertoni, Luca Corazzini.

A1. Invitation letters and reminders

All invitation letters and reminders were originally written in Armenian.

A1.1. Invitation letter template with the negative frame

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МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ
MINISTRY OF HEALTH

Patient's Name Surname: ……

Patient's Address: ……

Dear (Patient's Name and Surname),

The Ministry of Health, in collaboration with your general practitioner implements a screening program to prevent cervical cancer. Within the program, all women aged 30-60 residing in the territory of the Republic of Armenia are invited to undertake a PAP test examination. We urge you to read this letter carefully and consult with your general practitioner.

Please note that according to scientific studies missing cervical screenings can have negative consequences for your health, since cervical cancer can be discovered at more advanced stages. A lately discovered disease results in increased mortality, more extensive surgeries, and less effective treatments, with lower chances of recovery.

The cervical cancer PAP test examination **is free**.

Please visit your general practitioner during the dates mentioned below to undertake the PAP test examination.

General Practitioner: (general practitioner's name and surname)
Address: (the address of the primary healthcare facility)
Date: 3 June-7 June

Please bring this letter with you when visiting your general practitioner.

Sincerely,

(General Practitioner's Name and Surname)

General Practitioner

A1.2. Invitation letter template with the other-regarding frame

Patient's Name Surname: ……

Patient's Address: ……

Dear (Patient's Name and Surname),

The Ministry of Health, in collaboration with your general practitioner implements a screening program to prevent cervical cancer. Within the program, all women aged 30-60 residing in the territory of the Republic of Armenia are invited to undertake a PAP test examination. We urge you to read this letter carefully and consult with your general practitioner.

Your family members, relatives and friends expect you to live a long and healthy life with them. Detecting and curing a potential cancer at early stages can help you fulfil their expectations. Go to the screening for your loved ones!

The cervical cancer PAP test examination **is free**.

Please visit your general practitioner during the dates mentioned below to undertake the PAP test examination.

General Practitioner: (general practitioner's name and surname)
Address: (the address of the primary healthcare facility)
Date: 3 June-7 June

Please bring this letter with you when visiting your general practitioner.

Sincerely,

(General Practitioner's Name and Surname)

General Practitioner

A1.3. Invitation letter template with the neutral frame

Patient's Name Surname: ……

Patient's Address: ……

Dear (Patient's Name and Surname),

The Ministry of Health, in collaboration with your general practitioner implements a screening program to prevent cervical cancer. Within the program, all women aged 30-60 residing in the territory of the Republic of Armenia are invited to undertake a PAP test examination. We urge you to read this letter carefully and consult with your general practitioner.

Please note that scientific studies demonstrate that participating in cervical screenings can have positive consequences for your health and on the treatment of the diagnosed disease.

The cervical cancer PAP test examination **is free**.

Please visit your general practitioner during the dates mentioned below to undertake the PAP test examination.

General Practitioner: (general practitioner's name and surname)
Address: (the address of the primary healthcare facility)
Date: 3 June-7 June

Please bring this letter with you when visiting your general practitioner.

Sincerely,

(General Practitioner's Name and Surname)

General Practitioner

A1.4. Reminder template with negative frame

Patient's Name Surname: ……

Patient's Address: ……

Dear (Patient's Name and Surname),

The Ministry of Health, in collaboration with your general practitioner implements a screening program to prevent cervical cancer. Within the program, all women aged 30-60 residing in the territory of the Republic of Armenia are invited to undertake a PAP test examination. We urge you to read this letter carefully and consult with your general practitioner.

Please note that according to scientific studies missing cervical screenings can have negative consequences for your health, since cervical cancer can be discovered at more advanced stages. A lately discovered disease results in increased mortality, more extensive surgeries, and less effective treatments, with lower chances of recovery.

The cervical cancer PAP test examination **is free**.

With this letter we remind you to visit your general practitioner during the dates mentioned below to undertake the PAP test examination.

General Practitioner: (general practitioner's name and surname)
Address: (the address of the primary healthcare facility)
Date: 3 June-7 June

Please bring this letter with you when visiting your general practitioner.

Sincerely,

(General Practitioner's Name and Surname)

General Practitioner

A1.5. Reminder template with the other-regarding frame

Patient's Name Surname: ……

Patient's Address: ……

Dear (Patient's Name and Surname),

The Ministry of Health, in collaboration with your general practitioner implements a screening program to prevent cervical cancer. Within the program, all women aged 30-60 residing in the territory of the Republic of Armenia are invited to undertake a PAP test examination. We urge you to read this letter carefully and consult with your general practitioner.

Your family members, relatives and friends expect you to live a long and healthy life with them. Detecting and curing a potential cancer at early stages can help you fulfil their expectations. Go to the screening for your loved ones!

The cervical cancer PAP test examination **is free**.

With this letter we remind you to visit your general practitioner during the dates mentioned below to undertake the PAP test examination.

General Practitioner: (general practitioner's name and surname)
Address: (the address of the primary healthcare facility)
Date: 3 June-7 June

Please bring this letter with you when visiting your general practitioner.

Sincerely,

(General Practitioner's Name and Surname)

General Practitioner

A1.6. Reminder template with the neutral frame

Patient's Name Surname: ……

Patient's Address: ……

Dear (Patient's Name and Surname),

The Ministry of Health, in collaboration with your general practitioner implements a screening program to prevent cervical cancer. Within the program, all women aged 30-60 residing in the territory of the Republic of Armenia are invited to undertake a PAP test examination. We urge you to read this letter carefully and consult with your general practitioner.

Please note that scientific studies demonstrate that participating in cervical screenings can have positive consequences for your health and on the treatment of the diagnosed disease.

The cervical cancer PAP test examination **is free**.

With this letter we remind you to visit your general practitioner during the dates mentioned below to undertake the PAP test examination.

General Practitioner: (general practitioner's name and surname)
Address: (the address of the primary healthcare facility)
Date: 3 June-7 June

Please bring this letter with you when visiting your general practitioner.

Sincerely,

(General Practitioner's Name and Surname)

General Practitioner

A2. Additional Tables

Appendix Table A1. Balancing of individual pre-determined observable characteristics across treatment groups.

Dependent variable	(1) Age	(2) Urban resident	(4) Born in Quarter 2	(5) Born in Quarter 3	(6) Born in Quarter 4
Neutral Letter, No Reminder	0.147	0.002	0.002	0.007	-0.005
	(0.193)	(0.005)	(0.009)	(0.010)	(0.009)
Negatively Framed Letter, No Reminder	0.031	-0.002	-0.016*	0.005	0.009
	(0.195)	(0.005)	(0.009)	(0.010)	(0.009)
Other-regarding Letter, No Reminder	-0.204	-0.001	0.010	-0.001	-0.004
	(0.194)	(0.005)	(0.009)	(0.009)	(0.009)
Neutral Letter, Neutral Reminder	0.075	0.004	0.011	-0.019**	-0.001
	(0.196)	(0.005)	(0.009)	(0.009)	(0.009)
Neutral Letter, Negatively Framed Reminder	0.333*	-0.003	0.001	0.006	-0.009
	(0.194)	(0.005)	(0.009)	(0.010)	(0.009)
Neutral Letter, Other-regarding Reminder	0.145	-0.005	0.014	-0.010	-0.002
	(0.194)	(0.005)	(0.009)	(0.009)	(0.009)
Negatively Framed Letter, Other-regarding Reminder	0.229	-0.005	0.008	-0.006	-0.005
	(0.194)	(0.005)	(0.009)	(0.009)	(0.009)
Other-regarding Letter, Other-regarding Reminder	-0.051	-0.002	0.000	-0.008	0.020**
	(0.193)	(0.005)	(0.009)	(0.009)	(0.009)
P-value of an F-test for joint equality of all treatment effects	0.555	0.889	0.291	0.418	0.395
Mean Outcome, No Letter Control Group	44.33	0.782	0.227	0.273	0.249

Notes: The table reports tests for balancing of individual pre-determined observable characteristics across treatment groups. These are computed as ITT effects on the variable reported at the top of each column of belonging to each treatment group vis-à-vis the no letter control group. The mean outcome for this group is reported at the bottom of each column, as well as the p-value for an F test of joint equality of all treatment effects. OLS estimates with GP fixed effects. N = 36,196. Heteroscedasticity-robust standard errors reported in parenthesis. *: p<0.1; **: p<0.05; ***: p<0.01.

Appendix Table A2. Balancing of invitation week across treatment groups within the invited pool.

Dependent variable	(1) Invited in Week 2	(2) Invited in Week 3	(3) Invited in Week 4	(4) Invited in Week 5	(5) Invited in Week 6
Negatively Framed Letter, No Reminder	-0.014	0.005	0.005	0.012	-0.008
	(0.010)	(0.010)	(0.010)	(0.010)	(0.010)
Other-regarding Letter, No Reminder	-0.020*	0.014	-0.007	0.019*	-0.009
	(0.010)	(0.011)	(0.010)	(0.010)	(0.010)
Neutral Letter, Neutral Reminder	-0.010	-0.001	-0.005	0.021**	-0.007
	(0.010)	(0.010)	(0.010)	(0.010)	(0.010)
Neutral Letter, Negatively Framed Reminder	-0.017*	0.004	0.002	0.007	0.007
	(0.010)	(0.010)	(0.010)	(0.010)	(0.011)
Neutral Letter, Other-regarding Reminder	0.001	-0.005	0.011	0.006	-0.013
	(0.011)	(0.010)	(0.011)	(0.010)	(0.010)
Negatively Framed Letter, Other-regarding Reminder	-0.004	-0.003	-0.012	0.017*	0.004
	(0.011)	(0.010)	(0.010)	(0.010)	(0.011)
Other-regarding Letter, Other-regarding Reminder	-0.001	-0.006	-0.001	0.010	-0.002
	(0.011)	(0.010)	(0.010)	(0.010)	(0.010)
P-value of an F-test for joint equality of all treatment effects	0.251	0.591	0.494	0.463	0.521
Mean outcome, "Neutral Letter, No Reminder" group	0.175	0.166	0.168	0.155	0.170

Notes: The table reports tests for balancing of invitation week across treatment groups within the invited pool. These are computed as ITT effects on the variable reported at the top of each column of belonging to each treatment group vis-à-vis the "Neutral Letter, No Reminder" group. The mean outcome for this group is reported at the bottom of each column, as well as the p-value for an F test of joint equality of all treatment effects. OLS estimates with GP fixed effects. N = 20,642. Heteroscedasticity-robust standard errors reported in parenthesis. *: p<0.1; **: p<0.05; ***: p<0.01.

Appendix Table A3. First-stage effects of invitation letters and of letter and reminder combinations on letter reception and letter and reminder reception.

	(1)	(2)
Dependent variable	Letter reception	Letter and reminder reception
Parameter estimated	First-stage effects	First-stage effects
Estimation method	OLS	OLS
Letter only invitations	0.621***	-0.000
	(0.005)	(0.000)
Letter and reminder invitations	-0.000	0.542***
	(0.000)	(0.004)
Mean Outcome, No Letter Control Group	0	0

Notes: Column (1) reports the OLS estimates of the first-stage effects of being dispatched an invitation letter only or being dispatched a letter and a reminder combination on letter reception. Column (2) reports the OLS estimates of the first-stage effects of being dispatched an invitation letter only or being dispatched a letter and a reminder combination on letter and reminder reception. The dependent variable, the parameter identified, and the estimation method are reported at the top of each column, while the mean outcome for the no letter control group is reported at the bottom. The model controls for GP fixed effects. N = 36,196. Heteroscedasticity-robust standard errors reported in parenthesis. *: p<0.1; **: p<0.05; ***: p<0.01.

Appendix Table A4. ITT effects of invitation letters and of letter and reminder combinations on take-up, clustering standard errors by GP.

	(1)
Dependent variable	Screening participation
Parameter estimated	ITT - treatment dispatched
Estimation method	OLS
Letter only invitations	0.073***
	(0.006)
Letter and reminder invitations	0.098***
	(0.006)
P-value of an F-test for joint equality of all treatment effects	<0.01
Mean Outcome, No Letter Control Group	0.021

Notes: Column (1) reports the OLS estimates of the ITT effects of being dispatched an invitation letter only or being dispatched a letter and a reminder combination on screening participation. The dependent variable, the parameter identified, and the estimation method are reported at the top of Column (1), while the mean outcome for the no letter control group is reported at the bottom. The model controls for GP fixed effects. N = 36,196. Standard errors robust to clustering by GP reported in parenthesis. There are 81 GPs in the data. *: p<0.1; **: p<0.05; ***: p<0.01.

Appendix Table A5. ITT effects of invitation letters and of letter and reminder combinations on take-up, marginal effects from logit and probit model estimation.

	(1)	(2)
Dependent variable	Screening participation	Screening participation
Parameter estimated	ITT - treatment dispatched	ITT - treatment dispatched
Estimation method	Logit	Probit
Letter only invitations	0.101***	0.111***
	(0.005)	(0.006)
Letter and reminder invitations	0.118***	0.119***
	(0.004)	(0.004)
P-value of an F-test for joint equality of all treatment effects	<0.01	<0.01
Mean Outcome, No Letter Control Group	0.021	

Notes: Column (1) reports the ITT effects of being dispatched an invitation letter only or being dispatched a letter and a reminder combination on screening participation obtained as marginal effects from logit model estimation. Column (2) reports the ITT effects of being dispatched an invitation letter only or being dispatched a letter and a reminder combination on screening participation obtained as marginal effects from probit model estimation. The dependent variable, the parameter identified, and the estimation method are reported at the top of each column, while the mean outcome for the no letter control group is reported at the bottom. Each model controls for GP fixed effects. N = 36,196. Heteroscedasticity-robust standard errors reported in parenthesis. *: p<0.1; **: p<0.05; ***: p<0.01.

Appendix Table A6. ITT effects of invitation letters and of letter and reminder combinations on take-up, including only subjects who turned 30 from May 2017 onwards.

	(1)
Dependent variable	Screening participation
Parameter estimated	ITT - treatment dispatched
Estimation method	OLS
Letter only invitations	0.037***
	(0.012)
Letter and reminder invitations	0.062***
	(0.012)
P-value of an F-test for joint equality of all treatment effects	0.09
Mean Outcome, No Letter Control Group	0.030

Notes: Column (1) reports the OLS estimates of the ITT effects of being dispatched an invitation letter only or being dispatched a letter and a reminder combination on screening participation. The dependent variable, the parameter identified, and the estimation method are reported at the top of Column (1), while the mean outcome for the no letter control group is reported at the bottom. The model controls for GP fixed effects. The sample include only women born after May 1st 1987. N = 2,300. Heteroscedasticity-robust standard errors reported in parenthesis. *: p<0.1; **: p<0.05; ***: p<0.01.

Appendix Table A7. Heterogeneous effects by age (<50 years vs. 50+) and area of residence (urban vs. rural)

	(1)	(2)	(3)	(4)
Dependent variable	Screening participation	Screening participation	Screening participation	Screening participation
Parameter estimated	ITT - treatment dispatched	ITT - treatment dispatched	ITT - treatment dispatched	ITT - treatment dispatched
Estimation method	OLS	OLS	OLS	OLS
Sample	Age <50	Age≥50	Urban residents	Rural residents
Letter only invitations	0.074***	0.073***	0.063***	0.113***
	(0.004)	(0.006)	(0.004)	(0.008)
Letter and reminder invitations	0.094***	0.105***	0.087***	0.136***
	(0.004)	(0.005)	(0.003)	(0.007)
P-value of an F-test for joint equality of all treatment effects	<0.01	<0.01	<0.01	<0.01
Observations	23,652	12,544	28,246	7,950
Mean Outcome, No Letter Control Group	0.022	0.019	0.022	0.017

Notes: each column reports the OLS estimates of the ITT effects of being dispatched an invitation letter only or being dispatched a letter and a reminder combination on screening participation in the sub-sample reported at the top of the column. The dependent variable, the parameter identified, and the estimation method are reported at the top of Column (1), while the number of observations in the subsample as well as the mean outcome for the no letter control group is reported at the bottom. The model controls for GP fixed effects. Heteroscedasticity-robust standard errors reported in parenthesis. *: p<0.1; **: p<0.05; ***: p<0.01.